## CONTENTS

**RINECKER PROTON THERAPY CENTER**  
**THE GERMAN PROTON THERAPY CENTER**  
**FOURTH ANNUAL REPORT**  
**THE STATE OF THE ART IN RADIO ONCOLOGY**  
Experience from Treating the First 1,500 Patients.

<table>
<thead>
<tr>
<th>Page</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Introduction</td>
</tr>
<tr>
<td>7</td>
<td>The Patients’ Way through the Center</td>
</tr>
<tr>
<td>21</td>
<td>THE TEAM</td>
</tr>
<tr>
<td>22</td>
<td>Change of Guard: from Prof. Herbst to Prof. Bachtiary</td>
</tr>
<tr>
<td>24</td>
<td>Our Leadership Team</td>
</tr>
<tr>
<td>32</td>
<td>Our Scientific Advisory Board</td>
</tr>
<tr>
<td>41</td>
<td>THE TECHNOLOGY</td>
</tr>
<tr>
<td>42</td>
<td>The World of Proton Scanning - 2013</td>
</tr>
<tr>
<td>52</td>
<td>How Often Does the Patient Have to be Irradiated?</td>
</tr>
<tr>
<td>56</td>
<td>Problem: Cancer as Consequence of Radiation Therapy</td>
</tr>
<tr>
<td>63</td>
<td>THE THERAPY</td>
</tr>
<tr>
<td>64</td>
<td>Overview of Treatments at RPTC</td>
</tr>
<tr>
<td>70</td>
<td>Treatment of Children at RPTC</td>
</tr>
<tr>
<td>76</td>
<td>Results from 500 Patients Treated with Proton Therapy for Prostate Cancer</td>
</tr>
<tr>
<td>86</td>
<td>First Results of Proton Therapy for Pancreatic Cancer</td>
</tr>
<tr>
<td>92</td>
<td>Case Examples from RTPC</td>
</tr>
<tr>
<td>110</td>
<td>Contact / Imprint</td>
</tr>
</tbody>
</table>
The fourth operating year of ProHealth AG and RPTC was successful. The performance, with respect to both the number of cases and the technical quality, could be increased. Despite the challenging political environment for healthcare we were able to integrate the RPTC - as a service provider - more strongly into the German healthcare system; we were thus able to make proton therapy available for a higher number of patients.

We are delighted that the benefits of proton therapy are increasingly recognized and used by patients as well as health insurers and physicians. In particular since cancer, after cardiovascular diseases, is the second most common cause of death across the globe - and is still on the rise. Cancer, however, is not only a sociological problem. Costs associated with cancer burden the healthcare system and other fields of the European economy with approximately 120bn per year. Yet, only 36% of these costs account for the treatment itself. A further 36% arise from losses of income due to severe side effects from the therapy. Hence, from a sociological as well as economic point of view, there is a significant need for more effective and gentler cancer therapies, which deliver more successful healing processes while reducing the economic burden of cancer.

Proton therapy is a major step into this direction. In contrast to X-rays, protons release only little energy on their way to the tumor. Their maximum dose, which destroys the tumor cell, is only released at the end of the range of the proton beam, when protons stop (Bragg peak). Thus, this point, the location of the maximum dose, can be exactly determined in the third dimension through the speed of the protons (energy). The speed is calculated so that the protons will stop precisely at a previously determined point in the tumor. The healthy tissue behind the tumor is not exposed to any radiation; the tissue in front of the tumor is exposed to a considerably lower radiation dose compared to X-rays. In total the radiation exposure of healthy tissue can be reduced by more than two thirds with protons (compared to X-rays) at an equal or higher dose in the tumor. Proton therapy does not only offer greater chances of a successful recovery, but it also reduces the subsequent effects of radiation therapy by reducing acute and late side effects as well as the risk of secondary tumors. With regard to the example of prostate carcinomas, this means, in addition to outstanding medical results, a decrease in the duration of treatment of almost 50%, a reduction of acute and late side effects and normally no additional need for a rehabilitation program after the therapy. Higher treatment costs are offset by lower additional costs.

Even though the characteristics of proton beams were discovered as early as the beginning of the 20th century, and first medical tests were conducted among others in Harvard, USA, in the mid-1950s, the first proton therapy facility with complete hospital setting was established as late as 1990. To use this highly precise therapy optimally the medical imaging processes for diagnosis had at first to be developed sufficiently. Because, in contrast to X-ray irradiation, which is a “shoot through” method where precision involves only two dimensions, proton therapy requires three-dimensional planning. Only the technology of today enables this optimal use. Since then more than 95,000 people worldwide have received proton treatment. By now this therapy is considered the “gold standard” for an increasing number of indications, for instance with regard to the irradiation of children and tumors of the skull base. The global leaders in cancer therapy have either started the operation of proton therapy facilities (MD. Anderson, Massachusetts General Hospital (Harvard)) or the construction of proton centers (Mayo Clinics 2 facilities, Sloan-Kettering, John Hopkins, amongst others). The Arabian market has recognized the importance of this therapy as well. It is only Europe that is noticeably lagging behind.

The RPTC in Munich, Europe’s first fully clinical proton facility with complete hospital setting, is equipped with four full-motion gantries and one fixed beam for eye tumors.

It is, with the MD. Anderson Center (USA), world leading in cancer therapy, the only clinical facility which offers proton therapy in its fully-developed form, the scanning method. The RPTC does not only make Germany a global leader in cancer therapy, but with more than 1,500 patients treated (since 2009) it is the center with the world-wide largest experience in proton scanning, having already attracted patients from more than 44 nations. With the start of our operation we concluded a cost coverage contract with AOK Bayern and in 2011 with Debeke, Germany’s largest private health insurance company. Negotiations with other insurers are ongoing sucessfully to speed up the decision processes for compensation of treatment.

Let us do something to alleviate the immense suffering imposed on us by cancer.
THE PATIENTS’ WAY THROUGH THE CENTER

8  RECEPTION AND WAITING AREA
10  DIAGNOSTICS AND TARGET PLANNING
12  TUMOR BOARDS
12  MEDICAL CONSULTATION
14  PATIENT MANAGEMENT
15  PREPARATION OF IRRADIATION SESSIONS
16  THE IRRADIATION IN THE GANTRY
18  GUESTHOUSE
RECEPTION AND WAITING AREA

Upon their arrival, patients will receive all information necessary at the reception to enable them to find their way at the RPTC. The reception is also the point of contact regarding all questions during the course of treatment.
DIAGNOSTICS AND TARGET PLANNING

The first few days at the RPTC are used for detailed diagnostics and therapy planning. During the staging examination the entire body will be screened for signs of tumors and metastases. The examination involves a whole-body magnetic resonance tomography (MRI), sometimes in combination with a PET-CT (positron emission tomography), and is completely painless. If necessary, further examinations like endoscopy, ultrasound or angiography are performed. A high-resolution computer tomography (CT) is used for the following target planning. All equipment required is available at the RPTC to make the entire procedure as smooth as possible for the patient. In addition, all patients are offered a dose comparison with X-ray irradiation treatment to prove the superior dose distribution of proton irradiation.
TUMOR BOARDS

Since oncology consists of many different subject areas, specialists are integrated into the corresponding fields of treatment. For this purpose the RPTC has established a so-called Tumor Board with specialists for radiotherapy, radio diagnostics, surgery, oncology regarding internal medicine, urology as well as pathology. The Tumor Board will check each therapy decision and is involved in the process of target planning. Depending on the case, further specialists and, if possible, the referring physician are also involved.

MEDICAL CONSULTATION

The first medical consultation is a detailed talk with the patient. The therapeutic options, the indication for proton therapy, its side effects as well as the course of the treatment itself are explained in detail.
PATIENT MANAGEMENT

After the patients’ decision in favor of proton therapy, the department Patient Management will determine the dates for the irradiation sessions and will answer any further questions. It is here that patients will receive their individual irradiation schedules, information on the course of the treatment and a bracelet for further identification during the sessions. All patient-specific data is stored on this bracelet. The data is accessed electronically prior to each irradiation session to exclude any mix-up.

PREPARATION OF IRRADIATION SESSIONS

To optimally use the high precision of proton therapy it is important that the tumor is located at the same place during each irradiation session. For this purpose a bolus is produced prior to the first session. A mattress molded specially to the patient’s body is used for immobilization. Its vacuum system enables us to position the patient identically for each session.
The irradiation itself takes place in one of the so-called gantries. These weigh 150 tons, have a diameter of 11 meters and can revolve with sub millimeter precision around the patient (360° within one minute). The patient can thus be irradiated from medically optimal directions. In contrast to X-rays, protons can be targeted with utmost precision in all three dimensions. The beam can be guided with high-precision with deviations of less than 1 millimeter. The RPTC uses a special voxel to voxel modulated scanning procedure, the most highly developed form of proton therapy, to irradiate the tumor grid-like - with up to 25,000 target points. The penetration depth of the beam is steered with the adjustable proton speed. This is the only procedure that allows to strictly limiting the therapeutic dose - thus the maximum dose - to the tumor.

The number of irradiation sessions depends on the type and size of the tumor. On average a total of approximately 16 sessions (Monday to Saturday, once a day) can be expected. The entire irradiation session will typically only last for 15-20 minutes, whereas the irradiation itself takes only 60-90 seconds and is completely painless. Normally no more than 30 to 45 minutes should be planned for each session, including preparation. In some cases diagnostics and irradiation treatment are performed under short anesthesia - for instance for children who have generally trouble keeping still. Respiratory movements play also an important role with regard to tumors in the lung and liver. During a short anesthesia with oxygen feed the lung is brought into a controlled stable state, which allows the exact irradiation of the tumor. No oxygen deficiency will occur.
GUESTHOUSE

For maximum comfort our outpatients can book one of our elegant single or double bedrooms or a suite in the adjacent GUESTHOUSE AT THE RPTC. The guesthouse, which is located in a green belt directly next to the RPTC, offers all the amenities of an upscale 3-4 star hotel with several opportunities to unwind, like the quiet terrace, the hotel bar or the bright winter garden. Free magazines and the most current newspapers are available in the lobby. The guesthouse is further equipped with a gymnasium, a playground and a children’s playroom. The use of the internet is free of charge.
THE TEAM

22 CHANGE OF GUARD: FROM PROF. HERBST TO PROF. BACHTIARY
24 OUR LEADERSHIP TEAM
32 OUR SCIENTIFIC ADVISORY BOARD
The Medical Director of our „founding period“, Prof. Dr. med. Manfred Herbst is now actively involved in our Supervisory Board. His successor in the Medical Board is Prof. Dr. med. Barbara Bachtiary.

The RINECKER PROTON THERAPY CENTER was the first proton scanning facility in Europe which was constructed for patient treatment and not for research or experimental purposes. Similar forerunner facilities had been operated for years in the USA; in Germany, however, there was a lack of clinical experience with this therapy equipment. Yet the employment of American head physicians failed due to official regulations. Authorities seemed to doubt that nationalities with a different mother tongue can fully comprehend the German Radiation Protection Order.

At least university projects for proton therapy facilities were launched in many places in Germany. In 2000 the Bavarian state government refused the set-up of university proton therapy facilities – technically too complex, apparently not suitable for the personnel structures of local public institutions. Prof. Dr. med. Manfred Herbst was at the forefront of the university proton visionaries who had thus seen the failure of their visions for the future. We were very fortunate to welcome him aboard our company as Medical Director and Head of the Medical Board after he became an emeritus full professor for radiology of the University of Regensburg.

He helped us as counselor during the final stages of the construction of the center and often guided us when we had to tune the facility to the practical issues of a radio-oncological hospital. On 16 March 2009 Prof. Herbst treated the first patient in Europe with an all-electronic, fully developed proton scanning system at our facility. His commitment, his extensive clinical experience in radiology and his masterful intellectuality when using this advanced method have left a long-standing mark on our facility. The high radiation precision of our facility and its superior effectiveness changed the clinical operations, compared to all conventional X-ray irradiation methods, more than previously anticipated: the possibilities of treating with this extremely precise radiation therapy in a better way than before were hardly to envisage. Even today one quarter of our patients are cancer patients who had previously been treated unsuccessfully with X-rays (a therapy which could not be repeated due to the pre-exposure of the surrounding tissue) or patients for whom irradiation as the last effective means of treatment had to be refused at other facilities for technical reasons.

Prof. Herbst will not leave us; although he seems eternally young in body and spirit, in August 2012 he withdrew into our Supervisory Board. We are delighted to continuously have him on our side.

His successor is Prof. (University of Vienna) Dr. med. MSc Barbara Bachtiary. Prof. Bachtiary is from one of the largest radio oncological treatment centers in Europe at the Vienna General Hospital (Allgemeines Krankenhaus der Stadt Wien, AKH). She is an experienced radio oncologist, who chose for herself the step towards the further development of proton scanning. After treating by now 1,500 cancer patients with proton scanning at the RPTC, Prof. Bachtiary’s responsibility is now the integration of this proton therapy in the entire range of radio oncology. If nothing else, our collegial external relations and scientific cooperation projects, like the work with our Scientific Advisory Board, are important in this respect.

Contemporaneously with this replacement, we changed the head-physician structure in the center. Practical experience has shown that the maintenance times of this facility are conveniently short. This means that it can be run noticeably longer daily and weekly than would be reasonable for the working hours of only one responsible head physician. We did not want to temporarily replace the head physician routinely by only subordinated physicians. The center was therefore divided into two independent hospitals, headed by two radio oncologists – Dr. med. Alfred Haiderberger and Dr. med. Marc Walser. Both hospitals have to provide the full range of our irradiation treatments, yet some specialization of these two physicians is natural. In view of this structure it is important to have a linking joint above those two hospitals: as the Head of the Medical Board, Prof. Bachtiary is responsible for coordinating concepts of indication, quality controls and procedures between those two departments.

This corresponds to Prof. Bachtiary’s appointment to the Board of ProHealth AG, ensuring also the representation of medical matters in the management. The first months with this structure have shown that it works and ensures a high treatment quality, daily and weekly, throughout the entire operating time of the facility.

HEAD OF THE MEDICAL BOARD PROHEALTH AG

PD DR. MED. DR. MED. HABIL.
HEAD OF THE SUPERVISORY BOARD

BARBARA BACHTIARY
PROF. DR. MED.
HEAD OF THE MEDICAL BOARD PROHEALTH AG
Quality is our top priority. We have therefore not only a facility with the currently best irradiation technology available, but, in addition to our Scientific Advisory Board for the scientific support of our work, a team of experienced specialists from the fields of radio oncology, diagnostics, medical physics, anesthesia and quality management. Technology, scientific advice and highly competent physicians and physicists are working hand in hand to treat RPTC patients with the best possible radiation therapy. Please meet our leadership team:

**Associate University Prof. Dr. Barbara Bachtiary**

Medical Board of ProHealth AG

Since 2012 Associate Professor Dr. med. Barbara Bachtiary has been Head of the Medical Board of ProHealth AG. After her studies of biology and human medicine at the University of Vienna, in 2003 Prof. Bachtiary was appointed as specialist for radiation therapy and radio oncology by the Department of Radiation Oncology of the Medical University of Vienna. This was followed by a research stay in Canada until 2005 and then a position as senior physician for radio oncology at the Department of Radiation Oncology of the Medical University of Vienna. In 2006 she was habilitated and received the title of “Associate Professor”. In 2008 she was appointed to head the ambulance for Ear-Nose-Throat tumors at the Department of Radiation Oncology of the Medical University of Vienna before she transferred to the RPTC in 2011. In 2012 Prof. Bachtiary obtained the qualification for proton therapy.

- **1997 - 2003**
  - Department of Radiation Oncology of the Medical University of Vienna
- **Since 05/2003**
  - Specialist for radiation therapy
- **2003 - 2005**
  - Clinical Research Fellow, Department of Radiation Oncology, Princess Margaret Hospital, Ontario, Canada
- **2005 - 2011**
  - Senior physician for radio oncology at the Medical University of Vienna
- **Since 2008**
  - Head of the ambulance for ENT tumors
- **Since 06/2011**
  - RPTC in Munich
- **Since 04/2012**
  - Qualification for proton therapy
- **Since 2012**
  - Head of Medical Board of ProHealth AG
Dr. med. Alfred Haidenberger
Head of Radiation Clinic I

Since July 2012 Dr. med. Alfred Haidenberger has been head physician and Head of Radiation Clinic I at the RPTC. He completed his medical training at the University Hospital Innsbruck as specialist for radiation therapy. After gaining many years of experience as senior physician in the field of conventional radiation therapy, in 2010 Dr. Haidenberger obtained the qualification for proton therapy, which was awarded by the Bavarian Medical Association (Bayerische Landesärztekammer).

In Austria Dr. Haidenberger had been actively involved in several scientific panels and teams of experts. For nine years he was on the board of directors of the Austrian society for radio oncology/radiation therapy (Österreichische Gesellschaft für Strahlentherapie/Radioonkologie, ÖGRO); he is one of the founding members of the Tyrolean Working Group of Experimental Oncology (Tiroler Arbeitskreis Experimentelle Onkologie, TEXO). Since 2010 Dr. Haidenberger has been president of the society for future-oriented radio oncology (Verein Zukunftsorientierte Radioonkologie, ZORO).

Study of medicine in Innsbruck, 1999 MD
1999 - 2005 University Hospital Innsbruck for radio oncology
Since 12/2005 Specialist for radiation therapy
2005 - 2007 Senior physician for radio oncology at the University Hospital Innsbruck
2007 - 2008 Senior physician for radio oncology at the hospital Wiener Neustadt
2008 - 2010 Senior physician for radio oncology at the hospital Vöcklabruck
Since 07/2010 RPTC in Munich
Since 02/2011 Qualification for proton therapy
Since 2012 Head of Radiation Clinic I at the RPTC

Dr. med. Marc Walser
Head of Radiation Clinic II

Since November 2010 Dr. med. Marc Walser has been working as radiation therapist at the RPTC. In July 2012 he assumed the role of the Head of Radiation Clinic II. After his medical studies at the University of Zurich, he completed his medical training at the university hospitals Erlangen and Zurich as specialist for radiation therapy. Prior to his start at the RPTC he was employed in Amberg as senior physician and deputy head physician in the department of radiation therapy. In May 2011 Dr. Walser obtained the qualification for proton therapy.

Study of medicine at the University of Zurich, degree in 2002
2003 - 2006 Clinic and polyclinic for radiation therapy at the University of Erlangen
2006 - 2007 Clinic for radio oncology at the university hospital Zurich
2007 - 2009 Clinic and polyclinic for radiation therapy at the University of Erlangen
Since 11/2009 Specialist for radiation therapy
2009 - 2010 Radiation therapy at the hospital Gesundheitszentrum St. Marien Amberg
Since 11/2010 RPTC in Munich
Since 05/2011 Qualification for proton therapy
Since 2012 Head of Radiation Clinic II at the RPTC
Dr. med. Christian Zechmann  
Head of Diagnostics

Since 2013 Dr. med. Christian Zechmann has been the Head of Diagnostics at the RPTC. After his training to be a medical technical radiation assistant, Dr. Zechmann studied human medicine at the universities of Heidelberg and Mannheim. After passing the 3rd state examination he continued with the specialist training for radiology at the Medical Faculty Mannheim, the University of Heidelberg as well as the German Cancer Research Center in Heidelberg. At the latter he was employed as senior physician. He then decided to work for the department of nuclear medicine at the University of Heidelberg, focusing even further on the diagnosis of prostate carcinoma regarding the technologies of PET / CT (Cholin and Gallium-PSMA). After he obtained the qualification for nuclear medicine, he became Head of Diagnostics at the RPTC. Due to his work experience at the universities of Mannheim and Heidelberg as well as the German Cancer Research Center, he is contributing extensive expertise in the field of oncological radiology.

Dr. med. Morten Eckermann  
Head of Anesthesia

Since 2009 Dr. med. Morten Eckermann has headed the department of anesthesia at the RPTC. After his studies at the University of Regensburg and the Technical University of Munich as well as several years as assistant physician in the surgical ward, he started his specialist training at the group of municipal hospitals of Munich as anesthetist. Starting in 1999, he worked as senior physician in the department of anesthesia at the CHIRURGISCHE KLINIK DR. RINECKER, before he became the head of the corresponding department at the RPTC in 2009. He and his team conducted more than 2,700 anesthetics at the RPTC. The technology and results of the proton irradiation of tumors mobile during respiration with apnea under general anesthesia, which has only been realized at the RPTC on a global level, have been presented at various international congresses.

Study of medicine at the University of Regensburg and the Technical University of Munich

1989 - 1992 Assistant physician in surgical ward in general and accident surgery Plastic surgery with intensive care for severely burnt patients. Training to be a specialist for anesthesiology at the group of municipal hospitals of Munich

Since 08/1998 Specialist for anesthesia

1999 - 2009 Senior physician at CHIRURGISCHEN KLINIK DR. RINECKER

Since 2009 Head of Anesthesia at the RPTC

2004 University hospital Mannheim (institute for clinical radiology)
2004 - 2006 Department radiology at the German Cancer Research Center Heidelberg
2005 - 2006 Rotation to department radiology at the University Hospital Heidelberg, conventional X-ray diagnostics and angiography
2007 - 2008 Senior physician of his department at the Germany Cancer Research Center Heidelberg
Since 07/2008 Specialist for radiology
2008 - 2009 Senior physician at the German Cancer Research Center Heidelberg
2009 - 2012 Nuclear medicine at the university hospital Heidelberg
Since 05/2013 Head of Diagnostics at the RPTC
Markus Wilms
Head of Clinical Quality Management

Since 2009 Markus Wilms has been employed as senior physician at the Rinecker Proton Therapy Center in Munich. After his studies of human medicine at the University of Munich (Ludwig-Maximilians-Universität), he started work as assistant physician at a group practice for radiology in Ingolstadt. In 2004 he became specialist for radiation therapy. In 2009 Dr. Wilms obtained the qualification for proton therapy.

Study of human medicine at the University of Munich (Ludwig-Maximilians-Universität)
1998 - 2005 Assistant physician at group practice for radiology in Ingolstadt
Since 06/2004 Specialist for radiation therapy
2005 - 2009 Specialist at the RPTC
Since 06/2006 In charge of quality management at the RPTC
Since 05/2009 Qualification for proton therapy
Since 2009 Senior physician at the RPTC
Since 10/2011 Head of Clinical Quality Management

Christian Skalsky
Head of Medical Physics

Since December 2008 graduate physicist Christian Skalsky has been working as medical physicist at the RPTC since March 2010 he has headed the department of medical physics at the RPTC. After studying physics at the University of Regensburg and completing his degree dissertation on proton therapy at the clinic and polyclinic for radiation therapy and radio oncology of the University Hospital Regensburg, he was employed there as physicist. In 1996 Christian Skalsky started work as medical physicist at the institute for radiation therapy and nuclear medicine of the hospital of Rosenheim. During his time there, from 2000 to 2005, he acted also as lecturer for physics at the vocational college for nursing and health care. From 2004 to 2006 he was the responsible physicist for the technical restructuring of the institute for radiation therapy and nuclear medicine towards the medical care center at the hospital of Rosenheim for radiation therapy and nuclear medicine (Medizinisches Versorgungszentrum am Klinikum Rosenheim GmbH für Strahlentherapie und Nuklearmedizin). After the restructuring process he assumed the role of the leading medical physicist before he started working for the RPTC. From 2004 to 2008 Mr. Skalsky was also the consulting medical physics expert for nuclear medicine at the hospitals Bad Trissl Medical Centre and Inn-Salzach-Klinikum.

Study of physics at the University of Regensburg
1996 Medical physicist at the clinic and polyclinic for radiation therapy and radio oncology of the University Hospital Regensburg
1996 - 2006 Medical physicist at the institute for radiation therapy and nuclear medicine of the hospital of Rosenheim
2004 - 2008 Consulting medical physics expert for nuclear medicine at the hospitals Bad Trissl Medical Centre and Inn-Salzach-Klinikum
2006 - 2010 Medical physicist at the medical care center at the hospital of Rosenheim for radiation therapy and nuclear medicine (Medizinisches Versorgungszentrum am Klinikum Rosenheim für Strahlentherapie und Nuklearmedizin)
Since 03/2009 Qualification for proton therapy
Since 2010 Leading medical physicist at the RPTC
A further company highlight last year was the establishment of the Scientific Advisory Board. The RPTC succeeded in convening a circle of excellent advisors. The Board’s task is to scientifically accompany the RPTC’s clinical activities. The main objectives are a constant optimization of procedures and the definition of the RPTC as service provider within the field of radio oncology in Germany and Europe. It is necessary to define the effectiveness of proton therapy within the framework of the different treatment possibilities available today.

With more than 1,500 patients treated in four years, the RPTC has now not only irradiated a large number of patients – the highest number treated with all-electronic proton scanning globally – but it is now also equipped with meaningful data from follow-up processes. The Scientific Advisory Board was thus established now to evaluate our experience.

The members are outstanding personages from the fields of medicine and healthcare in general. The group of physicians and medical physicists is complemented by medical representatives of public health insurers to evaluate the proton scanning also from the cost carriers’ perspective.

Associate University Prof. Dr. Barbara Bachtiary
Medical Board of ProHealth AG

Professional career:

• Since 07/2012 Head of the Medical Board of ProHealth AG
• Since 04/2012 qualification for proton therapy
• Since 06/2011 specialist for radio oncology at the RPTC
• 2005 - 2011 senior physician for radio oncology at the Department of Radiation Oncology of the Medical University of Vienna; since 2008: head of the ambulance for ENT tumors
• 2006 habilitation: permission to teach radiation therapy and radio oncology
• 2003 - 2005 clinical research fellow, Department of Radiation Oncology, Princess Margaret Hospital, Ontario Cancer Institute, Toronto, Canada
• 01/2003 recognition as specialist for radiation therapy and radio oncology
• 1997 - 2003 assistant physician, training to be a specialist for radiation therapy/radio oncology at the Department of Radiation Oncology of the Medical University Vienna
• 1997 recognition as general practitioner (jus practicandi)
Prof. Dr. med. Christian G. Chaussy
Specialist for urology

Professional career:

• Study at university of Munich (Ludwig-Maximilians-Universität München), 1972 doctorate, afterwards at Institute for Surgical Research.
• 1975 development of extracorporeal shockwave lithotripsy, February 1980 treatment of first patient
• 1981 professor for urology in Munich, 1984 professor for urology at the University of California, Los Angeles, 1986 – 2010 head of urology at hospital Klinikum Harlaching in Munich
• Consulting professorship at University of Regensburg, professorship at Keck School of Medicine, California
• Since 1996 in Harlaching, treatment of prostate cancer with ultrasound (high frequency focused ultrasound, HIFU).
• Further distinctions: Maximilian Nitze award of German society for urology (Deutsche Gesellschaft für Urologie), Ritter von Frisch award from this society as well. Lifetime Achievement Award of End urological Society and president of this society since 2012, honorary member of Royal College of Surgeons Edinburgh, honorary professorship at Beijing Medical University, honorary member of Chinese urological society.

The treatment of prostate carcinomas is currently very competitive: replacement of operative prostatectomy by X-ray irradiation. Attempt of extreme hypofractionation with photons - as with protons. We are delighted to have found a globally esteemed urologist with Prof. Chaussy, who can advise us on the dose selection for prostate irradiation.

Jürgen Malzahn
Head of department for inpatient care/rehabilitation in the national association AOK-Bundesverband, Berlin

Professional career:

• Since 2007 head of department for inpatient care/rehabilitation in the national association AOK-Bundesverband, Berlin
• 2000 - 2007 transfer to department for hospitals of AOK-Bundesverband and assistance in DRG system
• 1997 - 2000 department for hospital case management of AOK-Bundesverband
• Study of human medicine in Berlin and Frankfurt am Main

Jürgen Malzahn is the representative of AOK, the largest single supplier for public health insurance, operating throughout the entire Federal Republic. AOK is an important partner of RPTC to make proton irradiation available for publicly insured patients.
Prof. Dr. med. Oliver Micke
Head physician of the clinic for radiation therapy and radio oncology at Franziskus Hospital, Bielefeld

Professional career:
• Since 2006 head physician at the clinic for radiation therapy and radio oncology at Franziskus Hospital, Bielefeld
• Senior physician at clinic and polyclinic for radiation therapy- radio oncology, university hospital Münster
• Scientific and clinical training at university hospital Münster, Memorial Sloan-Kettering Cancer Center in New York and Karolinska Cancer Center in Stockholm, Sweden

Dr. Micke is an authority on the irradiation of pancreas carcinoma as well as neuro-oncology. In particular proton therapy with the scanning method has lead to new successful therapy concepts for pancreas carcinomas at the RPTC. The irradiation of tumors in the area of the skull and spinal column is also internationally regarded as the classical domain of proton therapy.

Dr. med. Klaus-Peter Thiele
Deputy head of the center of competence for oncology of MDK (Medizinischer Dienst der Krankenkassen, medical services of health insurers), MDK North Rhine

Professional career:
• Since 2000 deputy head of the center of competence for oncology; MDK Nordrhein
• Assistant physician university hospital Düsseldorf, department hematology, oncology and clinical immunology

As deputy head of the center of competence for oncology of MDK, MDK North Rhine, Dr. Thiele is also member of the Federal Joint Committee of physicians and health insurers (Gemeinsamer Bundesausschuss der Ärzte und Krankenkassen, GBA). He was assigned to the Scientific Advisory Board by AOK Bayern. Dr. Thiele plays thus a highly important role in integrating proton therapy into the German public healthcare system.
Prof. Dr. rer. nat. Jan J. Wilkens
Head of medical physics at the clinic for radiation therapy and radio oncology, Technical University Munich (Technische Universität München)

Professional career:
• Since 2009 associate editor – „European Journal of Medical Physics“
• Since 2008 W2 professor for subject “Advanced Technologies in Radiation Therapy” Technical University Munich
• 2004 - 2008 research associate at the German Cancer Research Center
• 2006 post-doctoral research associate at the Washington University in St. Louis
• 2005 recognition for medical physics of German society for medical physics (Deutsche Gesellschaft für Medizinische Physik e.V., DGMP)
• 2003 research fellow at the Massachusetts General Hospital, North-East Proton Therapy Center (NPTC), Boston (USA)
• 2001 - 2004 doctorate in physics at University Heidelberg (summa cum laude)
• 2000 - 2002 study of medical physics and technology at University of Kaiserslautern
• 1995 - 2001 study of physics, University of Munich and University of Nottingham; doctorate

Prof. Dr. Wilkens has distinguished himself in many years of experience in the field of particle therapy with different types of ions as well as his research focus on the technical development of proton acceleration. Due to the sophisticated and complex technology of proton scanning at the RPTC, medical physics has a special standing in this regard.

Prof. Dr. med. Normann Willich
General manager of DEGRO (Deutsche Gesellschaft für Radioonkologie, German society for radio oncology)
Head of registry for recording late effects of radiation treatment in children and adolescents (Register zur Erfassung radiogener Spätfolgen bei Kindern und Jugendlichen, RISK)

Professional career:
• Since 2011 general manager of DEGRO (Deutsche Gesellschaft für Radioonkologie, German society for radio oncology)
• 1991 - 2011 director of polyclinic for radiation therapy and radio oncology at the University of Münster
• 1989 habilitation in Munich
• 1981 - 1989 training radio oncology Medical School, University of Munich
• 1981 doctorate in Augsburg
• 1976 - 1981 further training in surgery and radiology in Augsburg
• 1974 - 1975 medical residency in pediatrics, neurology/psychiatry
• Anesthesiology, internal medicine, surgery in Berlin, Oberhausen, Kiel, Augsburg, Germany
• 1967 - 1974 study of medicine at the University of Kiel

Prof. Willich is a renowned expert for radio oncology for children and head of the registry for recording late effects of radiation treatment in children and adolescents (RISK). Proton therapy is nowadays regarded as the gold standard in treating children.
How often does the patient have to be irradiated?

Problem: Cancer as consequence of radiation therapy.
SUMMARY FOR PATIENTS:
In contrast to Roentgen, proton scanning allows to target the beams in all three dimensions. This means that radiation damages in the surrounding area can be avoided, allowing a higher tumor dose. The physical advantage of proton irradiation can only be fully used with the technical scanning method, as realized at the currently worldwide most effective facility, the RPTC in Munich. The advantages for the patient are the absence of side effects, the damage to healthy tissue. However, this means that in clinical practice the X-ray therapy – cannot occur. On the one hand this means that the development of resistances – a major issue in chemotherapy – cannot occur. On the other hand, however, this means that in clinical practice the X-ray dose applicable for the tumor is regularly limited by the side effects, the damage to healthy tissue.

THE DECISIVE STEP:
FROM X-RAYS TO PROTONS
If tumors are detected and treated early enough during the course of the disease, i.e. if not yet an extensive metastatic spread has occurred, these failures can generally be ascribed to a basic characteristic of X-rays, which even most modern therapy forms like intensity-modulated radiation therapy (IMRT) or those methods often known under their product names (Cyberknife, Rapid Arc) cannot fully overcome.

X-rays are electromagnetic waves, like light, only with a shorter wave-length, richer in energy and much more penetrating. Their effect is to destroy the electric balance of molecular components in the body’s tissue (ionization) and to thus induce the creation of “radical” molecule fragments, which damage the genetic material of the cell and cause it to die-off. X-rays are absorbed during this physical process, quasi soaked up and this causes the rapid decrease in local strength, the local dose in the body. This means that the dose is always highest underneath the skin; it has already declined in the deeper located tumor; healthy tissue behind the tumor still receives radiation. In other words: X-rays are two-dimensional, they can be aimed up and down, to the left and right, but not in the beam direction, the third dimension.

This situation is highly unsatisfying: each irradiation with X-rays leaves a trail of destruction through the body; a concentration within the tumor which is surrounded by healthy tissue is not possible. It should be taken into account that all radiation effects, in contrast to chemotherapies, are not tumor-specific. They have the same damaging effect on healthy tissue as well! This may have the advantage that every tumor, if its location is known, could be irradiated effectively: While all cells have a repair mechanism for radiation damages with differing degrees of effectiveness, they may be overpowered with technically simple dose increases. On the one hand this means that the development of resistances – a major issue in chemotherapy – cannot occur. On the other hand, however, this means that in clinical practice the X-ray dose applicable for the tumor is regularly limited by the side effects, the damage to healthy tissue.

How is it thus possible to, so to speak, extract the tumor with X-rays from its surroundings? By simply irradiating it concentrically from different directions. This has been optimized with the more modern methods mentioned above. Yet in all cases the achievable concentration in the tumor with X-ray irradiation from many directions does only mean a replacement of the dose level in the healthy tissue by the amount of healthy tissue irradiated. In simple terms this means that the healthy cells in the surrounding area will receive a lower dose, but the number of healthy cells affected is higher. This unavoidable increase in the irradiated volume should not be taken lightly: Each nonlethal irradiation of a cell will also pose the risk of a later tumor induction due to this irradiation: see below „Problem: Cancer as Consequence of Radiation Therapy“. A “bath in X-rays” will also cause numerous individual side effects. For instance, when irradiating tumors in the neck area more or less all salivary glands are affected, a very burdensome treatment effect; or in cases where a high volume of healthy brain parts are included, which, particularly in children, will later cause intelligence defects and much more.

In 1946 nuclear physicist Robert Wilson suggested to bypass these shortcomings of X-ray therapy by using a rather exotic seeming physical effect: In 1905 the British physicist William Henry Bragg discovered the following effect in protons: protons are the per se harmless atomic nuclei of hydrogen, the most common element in cosmos and humans (not to be confused with the so-called photons, the energy packets of electromagnetic radiation, thus of light and Roentgen, termed that way by Einstein). If complex radiation sources, the cyclotrons or synchrotrons that
work with electromagnetic energies, are used to accelerate protons to very high speeds (up to 180,000 km/sec at the RPTC) they can penetrate the human body with a depth of up to 38cm. They are also ionizing and have thus a generally similar effect on cells like Roentgen. Because of their initially rather low ionization due to their high speed they are not absorbed, but simply slowed down and the slower they get the more they distort the atomic electron shells, and the more they are slowed down. This braking process will escalate in a sharp peak of local ionization.

The location of this Bragg peak, this peak of ionization, can thus be adjusted in depth by simply determining the speed of the protons (figure 1). Finally, an irradiation treatment which may be targeted not only in two, but three dimensions, and can hence be concentrated in the tumor! For patients this means that they are freed of the penetrating character of X-rays; behind the tumor (viewed in the beam direction) there is no radiation impact and in front of the tumor the radiation dose is, in contrast to Roentgen, not higher, but lower (figure 2).

We realize that the efficiency of irradiation methods is simply dependent on how many healthy cells are damaged to sterilize one tumor cell or, in other words, the dose ratio target area to healthy surrounding area. Of course, these figures depend on the anatomy given; on the ratio tumor volume to girth in the irradiation area. In practice all X-ray methods give off the approximately three to fivefold amount of tumor dose into the healthy surroundings. With protons, subject to the method used, see below, a ratio of one to one or even better is achieved.

Radiation therapists have not yet reached the “promised land”, but they have come a long way.

THE OPTIMIZATION: FROM PROTON SCATTERING TO PROTON SCANNING

The use of protons for cancer irradiation was first implemented with a targeting method nowadays referred to as scattering system. For the majority of the 95,000 patients treated with protons worldwide this
scattering system was used; the facilities are in use and, until quite recently, were still taken into operation. No manufacturer is offering them for the future. From a historical viewpoint, it is hard to understand why this method was chosen at first. The alternative, the just recently implemented proton scanning is, after all, based on a venerable technology: the steering procedure for the electron beams in the dated tube television sets.

The radiation sources (cyclotrons or synchrotrons) deliver the protons as a pencil-thin beam, which is passed on to the patient in this form, in vacuum tubes belted by magnets. During the scattering process this beam is first sent through spokewheel-formed filters, which adjust the Bragg peak successively for the different layers of the tumor by slowing down the protons at different rates. Afterwards one or two further specially formed filters are passed to evenly spread the beam over more or less large irradiation fields. The third filter is then passed, which consists of an edge-defining aperture and a shaped plastic wedge, which reflects the rear wall of the tumor (viewed in the beam direction) (figure 3).

This complex equipment causes a number of disadvantages and problems:

• The limiting aperture and the filter for the tumor-conformal adjustment have to be shaped individually for each field and for each patient, i.e. also several times for one case. This gives rise to delays between gathering production data during therapy planning and the start of irradiation treatment and is thus increasing the risk of position changes in the tumor (growth) or the surrounding area (losses in weight and volume).
• The entire machinery has to be exchanged for each patient and each change in fields to which purpose the heavy beam-guiding equipment (the so-called gantries) have often to be brought into a zero-position. This stalls the duration of treatment and means that the staff is exposed to radiation since the apertures, if used frequently, become radioactive for a brief time.

And for the patient:
• Whenever accelerated protons meet matter, i.e. the filters, they collide with atomic nuclei, which results in neutron radiation. This is partly concentrated towards the patient. The amount of these emission losses may be small, but: (hereafter doses are stated in Gray, these are absorbed dosages). With regard to protons, which will not leave the body, Gray correspond to, by definition, approximately the Sievert doses, which state the irradiation dose and are normally used for quantifying the radiation hazard. In case of a therapeutic local dose of up to 80 Gray, the neutron dose accounts for “only” 0.3%, after all an approximate neutron dose of 240 Millisievert, which affects the patient’s body. From as little as 5,000 Millisievert (extensive partial-body irradiation) significant bodily harms with lethal consequences occur. See below: „Problem: Cancer as Consequence of Radiation Therapy”.
• The decisive disadvantage of the scattering system is that with the shaped bolus the dose stop can be adjusted to be very exactly “in line” with the rear wall of the tumor (seen in the beam direction). In case of a tumor which is not evenly distributed over the depth, i.e. which is somewhat cube-shaped, this procedure will inevitably lead to frontal extensions of the tumor dose (figure 4).

• This is still better compared to Roentgen, where the dose in the front is naturally higher than the tumor dose, but is highly detrimental in comparison with the scanning procedure.

The undisputedly best proton application form (from a technical and radiobiological perspective) is the scanning procedure (synonym pencil-beam scanning, grid scanning and others). This works with quasi zero mechanical effort, but with a complex electronic con-
trol, which employs beam bending by heavy magnets (at RPTC 0.8 to). With initially high and then lower speeds the pencil-thin beam is steered in a meander-shaped pathway over the tumor with magnetic deflection. Magnets are used for both the X and Y axes. This process is repeated depth layer by layer; the depth is controlled through the proton speed, which is adjusted at a distance from the patient. This results in individual, overlapping spots, whose spacing is adjusted exactly to their size. In case of a very large tumor (5.5 l at the RPTC) 25,000 spots are swept in one irradiation session. The electronic equipment controls and archives the dose for each individual spot. The dose distribution is thus completely freely adjustable for each single spot. For each region of the tumor the dose can be chosen freely; each dose distribution can be modeled (even the local dose curve of X-rays could be simulated) (figures 5 and 6). The decisive advantage for the patient is:

- There is no significant neutron burden for the entire body.
- There are no front extensions of the tumor dose.

This is nowadays the only procedure which ensures that patients are spared optimally, simultaneous with the optimal dose in the tumor, by limiting the therapeutic dose only to the required target volume. At the RPTC the precision in the depth layers, in the Z axis, lies at 0.5 millimeters due to the electronic steering and monitoring processes. All even small tolerances in the beam delivery are limited to 1.0 millimeters.

Figure 5: During scanning the proton beam is moved in a meander-shaped pathway to the positions calculated in the therapy plan - scanned. This is repeated for each depth layer, which means that the tumor is swept three-dimensionally. The blue dots in the figure correspond to the centers of the spots; the connecting lines show the movement of the beam.

Figure 4: Illustration of the dose extensions during the scattering procedure. It shows therapy plan comparisons calculated for homogeneous bodies with a globular tumor on the one hand and a triangle-shaped tumor on the other hand.

Dose extensions during the scattering procedure
in the X and Y axes by a steering adjustment of the scanning magnets. The deviation of the spot-to-spot dose is below 5%. The homogeneity of dose distribution is better than 2% of the dose.

With the fully-electronic scanning system proton irradiation has reached its maturity. Which systems are currently available worldwide?

• The RPTC in Munich is named as an example
• The facility of the Scripps University in San Diego, California will start operation in 2013 with precision values of the same magnitude.
• MD Anderson in Houston, USA, the global number one in cancer therapy ranking is also operating a modern scanning facility with, for technical reasons, a somewhat wider beam.
• The research facility of Paul Scherrer Institute in Villingen, Switzerland - the scanning pioneers – uses a partial scanning system, which electronically controls the X and Z axes; a mechanical transport of the whole patient is used for the Y axis.
• A fully-electronic scanning system is used at the German Cancer Center in Heidelberg. Since the facility’s technical design was primarily devised for heavy ions, not protons, the precision values mentioned above are not reached.
• Facilities with the so-called “uniform scanning” have principally no scanning systems. Only the filters for spreading the beam are replaced by a fixed electronic “wobbling” of the beam.

**Bibliography:**


HOW OFTEN DOES THE PATIENT HAVE TO BE IRRADIATED?

THE SECRETS OF HYPOFRACTIONATION

SUMMARY FOR PATIENTS:

More recent analysis procedures for the necessity of treatment repetitions - today up to 41 times - have shown the same success with a significantly reduced number of daily irradiation sessions and thus a significantly lower treatment duration. This applies to both X-ray and proton irradiations. The proton-scanning typical beam concentration in the tumor facilitates a shortening of treatment times since in this case healthy tissue is spared primarily due to the local concentration of the radiation. The RPTC has already reduced the common number of sessions for prostate carcinoma of 41 to 21, for instance. We are working cautiously to shorten the treatment times even more – the higher tumor-sterilization effectiveness of shorter treatment times even more – the higher.

We have shown that we can reduce the common number of sessions for prostate carcinoma of 41 to 21, for instance. We are working cautiously to shorten the treatment times even more – the higher.

Naturally it is important for all patients how often they have to be irradiated, i.e. how long their cancer treatments will take. Irradiation sessions will normally take place once a day. Procedures with several sessions during one day were tested, but could not gain acceptance. While a chain of daily irradiation treatments without breaks seems sensible in theory, a spacing of treatment sessions is common practice: five weekdays followed by two days without treatment on weekends. The RPTC is aiming for a six plus one solution in the long term – considerations, which also depend on operational conditions like time required for maintenance work, etc.

How many single irradiation sessions can patients now expect? The number ranges from 3 to 41 sessions. To explain this surprising variety we are exclusively concentrating on radiobiological aspects. There are unfortunately also others: While payment for proton irradiations of publicly insured patients in Germany has been enforced in the form of lump sums per case - this is not yet valid for all privately insured ones - treatment sessions in the USA are remunerated separately. The virtually only divergence from the lump compensation norm in Germany is the payment of X-ray irradiation sessions in groups, i.e., dependent on their number. It is therefore beneficial for the operator to carry out as many single irradiation sessions as possible for one and the same patient. But let us not concentrate on this.

Special aspects apply for the irradiation of brain tumors, which require a high number of individual sessions: the brain parts irradiated may swell, even if minor, which can have a negative impact in the brain case confined by bones. This does not apply to other tumors in the body.

So far tumors with a volume of up to 5.5 I have been irradiated at the RPTC. This is, however, an exception. To expose such a large number of cells to a practically single-shot sterilization would probably overstrain the body’s existing tissue decomposition systems.

Most tumors, nevertheless, generally a lot smaller, could be killed in one session. With the exception of those special cases, the fractionation of the irradiation effect into different sessions on different days may only be justified with the attempt of granting healthy tissue radiated a chance of recovery between the individual treatment sessions. This may affect tissue in the target area which cannot be spared or tissue in the entrance area of radiation, or, in case of Roentgen, also in the area behind the tumor where the beam exits.

Since in the case of protons, as outlined several times, the radiation dose in the inflow area is lower compared to Roentgen, and no radiation is given off behind the tumor, the necessity of these frequent irradiations will have to be discussed anew. In case of the modern method of proton irradiation, the proton scanning as performed at the RPTC, no tumor dose is given off anywhere outside the targeted area (in contrast to the prior scattering method for protons). This raises again the issue of when the radiation dose should be split, why it is still useful, and to which extent: 3 or even 41 times?

The decisive question is always which tissue, healthy or tumorous, will recover at which rate. The recovery mechanisms are known. The vascular supply to the tumor plays a little discussed role. Almost all cells including the tumor cells are dependent on the supply from directly adjacent small blood vessels, the capillaries. The distance of the cell to the next vessel is generally only 200 micrometers. The tumor can thus only extend beyond the microscopic scale if it succeeds in inducing the blood vessel system with messenger substances to create new vessels. Blood vessels, possibly those grown shortly, are sensitive to radiation. For instance irradiation of hemangioma can cause a thrombosis, an occlusion. This insufficiently studied mechanism itself would speak for keeping the number of irradiation sessions as low as possible, but with high single doses. Apart from this mechanism, every cell has an extremely successful repair procedure that fixes the crucially hit cell component, the genetic material. The genetic material, the DNA, occurs during its predominant rest period in so-called double strands, which wrap around each other spirally. The genetic information is in duplicate, stored in both of the closely connected strands: the molecules forming the code in the rungs of this twisted ladder complement each other. There are enzymes which, in case of a radiation-induced destruction of one of
these strands, repair the affected strand with a fidelity of 1:20,000 according to the information stored in the second strand. If this mechanism did not exist, we would not be able to sunbathe. The DNA of our skin cells would be damaged too heavily. Even double-strand breaks are repaired enzymically with the information of the second chromosome, however, with a lower fidelity of 1:20.

The repair mechanisms, working with a different precision rate in each cell type, determine the radiation sensitivity or resistance (this can be easily compensated with a higher radiation dose in tumors) of the different healthy or tumorous tissues. Radiation biologists have done their utmost to test this repair capacity, i.e. the radiation sensitivity, for each single tissue.

To understand all this, we have to immerse into a complex field of radiation biology. The ratio between physical radiation dose and biological effect can be expressed with the percentage of cells of a cell culture, for instance, but also of human tissue, that die off at a certain dose. As many relationships, this results in an s-shaped curve: with increasing radiation intensity only little happens at first; the minor damages are repaired solidly, but then a dose-related, so-called linear increase in effect occurs. A significantly higher dose (square increase) is then required to sterilize the last percent or promille of the cells. Without directly explaining a causal relationship mathematically, which can be reproduced with a mathematical term, which (for those keen on formulas) looks as follows:

$$P = e^{-N_0 e^n(-\alpha D - \beta D^2)}$$

Formula 1: Probability P for the clinical effect (e.g. tumor control) at a daily dose of D, n fractions, an amount of tumor cells of N₀ and the tissue parameters α and β.

With this alpha/beta ratio the radiation sensibility of tissue is now quantifiable. It is extremely diverse, here some examples:

• Healthy tissue 6-10 Gray
• Majority of carcinomas 10 Gray
• Prostate carcinomas 1.5 Gray

The higher the figure, the more sensible it would be to split the required radiation dose into many single irradiation sessions, i.e. to hyperfractionate. In the case of lower ratios, however, the number of sessions should be as low as possible, but involving higher doses: hypofractionation.

The figure above for prostate tumors in particular speaks for hypofractionation. The cautious fractionation of the irradiation dose into different sessions, however, will also result in – biological – costs (another formula) according to these mathematical considerations:

$$EQD^2 = nD \frac{D + \frac{\alpha}{\beta}}{2 + \frac{\alpha}{\beta}}$$

Formula 2: The biologically equivalent dose to a single dose of 2 Gray EQD, depends both on the number of fractions n, the adjusted daily dose D and the figures α and β, depending on the tissue.

The formula simply shows that, dependent on this tissue-typical alpha/beta ratio, when fractioning the irradiation into several sessions, a higher calculated overall dose is always necessary, and in fact, again depending on this figure, a considerably higher dose under certain circumstances. To express this, the term effective dose was coined. With regard to the example of prostate carcinoma this means the following:

• For 41 irradiation sessions a physical overall dose of 82 Gray (as reference standard) is needed to achieve an adequate therapeutic safety.
• For 21 fractions, as applied at the RPTC, a physical dose of only 63 Gray is needed to achieve the same therapeutic safety of an effective dose of 82 Gray.
• In case of an extreme hypofractionation of only five sessions only a physical dose of 35 Gray would be needed for an effective dose of 82 Gray.

The available literature on hypofractionation has currently actually proven on 1,100 American patients that the reduction of 41 irradiation days to only five has shown at least equally satisfying results. This refers to Roentgen. The future of protons is also – cautiously – developing into the direction of this hypofractionation. Since the physical dose, which is emitted into healthy tissue during proton therapy, accounts for only 1/3 to 1/5 of the inevitable harmful dose with X-rays, depending on the patient’s anatomy, such a hypofractionation with protons should be possible with the utmost patient safety and protection.

Bibliography:

All forms of exterior radiation therapy use ionizing radiation as therapeutic means. This causes the creation of so-called chemical radicals in all living cells, which damage or sterilize the cell. The radiation effect, however, does not differentiate between tumorous and healthy cells, which, on the one hand, prohibits the generation of resistance of cancer cells to the therapy but, on the other hand, limits the dose applicable to the cancer itself due to radiation side effects. This occurs because none of the therapeutic methods used allow the absolute concentration of radiation in the tumor.

To improve the range of applications and effectivity of radiation therapy numerous methodological advances were implemented into therapy, particularly in more recent times. With regard to the X-ray treatment with electromagnetic radiation, the alignment of the target area to the tumor shape was optimized by exactly shaping the beam cross-section (multileaf method). Since the exponential dose decline in the third dimension, the direction of the beam itself, cannot be changed in electromagnetic radiation, it has been tried to achieve a clinically advantageous radiation concentration in the tumor and target area by bundling the irradiation from more and more directions (e.g. Cyberknife) and careful differential dosing of these different beams (intensity-modulated radiation therapy, IMRT). Yet then only the dosage level is replaced by the volume of healthy surrounding tissue irradiated: the ratio between effective radiation in the tumor and overall harmful radiation in the healthy surroundings depends only on the body geometry and cannot be improved with Roentgen methods.

With protons the additional targetability regarding the beam direction, the third dimension, is exploited with the phenomenon of Bragg peaks. No tissue behind the tumor is irradiated; the dose in front of the tumor is lower, not higher than in the tumor itself, like with X-rays. Albeit in the early proton techniques (scattering or the so-called uniform scanning method) this was achieved by controlling the particle beam with numerous mechanical apertures. This procedure enabled a significant concentration in the tumor, but the form adjustment of the target area was only possible for the rear wall of the tumor, away from the radiation source; in the front the high tumor dose was still given off into healthy tissue. The aperture-based shaping of the proton beam did also create a neutron radiation, which spread in the patient’s body far beyond the target area. See above “The World of Proton Scanning – 2013”.

The harmful radiation occurring in healthy tissue when applying the different methods may not be neglected. In the case of the X-ray methods in particular and in small areas in front of the tumor (with proton scattering), the entire tumor dose extends into healthy tissue. When using the common two-field (beam direction) irradiation of prostate carcinomas with X-rays, e.g. from both sides of the body, the entire body portion hip joint / prostate / opposite hip joint receives the same dose as the tumor. Please see dose images below in “Example Cases” for comparison. With naturally large fluctuation margins unwanted dose regions of more than perhaps 40 Gray may occur in healthy tissue during routine X-ray irradiations. These doses are only nonlethal (table 1) because the irradiation areas comprise only parts of...
...during the radiation therapy. The term includes also radiation-induced tumors in the connective tissue, which should be termed sarcomas from a histological point of view. The clinical observation of such late carcinomas, which may occur after years, leads, as early as 1999, to the recommendation to stop X-ray treatment of children and adolescents, but to treat them instead with proton methods.3

Yet it was difficult to quantify the real risk of secondary carcinomas. This not least because late carcinomas occurring close to the original tumor are seen as tumor recurrence without classifying them exactly with histological tissue samples.

In recent times the risk of secondary tumors was quantified by exactly analyzing the dose values in healthy tissue.4 The dose calculation system of the so-called Monte Carlo method was used for this purpose. In doing so the path of individual photons in the case of Roentgen or protons is observed at high computational costs. This delivers a very accurate statistical picture of dose distribution. The local dose distribution with Roentgen and the above-mentioned neutron release with protons were both taken into account. The probability of carcinogenesis was calculated for the individual organs affected.

The irradiation of a child with an extended field (field size 50 x cm²) along the spinal cord was used as typical example. A life expectancy of 73 years was taken as a basis. This case constitutes thus the ceiling for the tumor risk to be expected. The percental risks per life year are shown in table 2. The cumulative risks at a life expectancy of 73 years are cited in table 3. The difference between the various dated and more modern (IMRT Roentgen methods) in tumor risk are thus made clear, as well as the significantly lower risks of proton treatments. The improvement of proton scanning compared to the scattering method can be ascribed to the elimination of approximately 90% of...
the neutron irradiation generated during scattering (a range of 250 millisievert) as well as to the absence of the high-dose extension in front of the tumor during scattering.

These analyses are, as shown, purely mathematical procedures, which precisely render the actual local dose distribution. The underlying ratio between the dose received - in the low-dose range - and the risk of late carcinomas itself is much less certain. These data are based on the analysis of numerous radiation damages, which, however, were mostly gathered during wartime conditions (Hiroshima, Nagasaki) or accidents (including Chernobyl and recently Fukushima). The problem under these circumstances was to exactly reconstruct the dose received. Too pessimistic or optimistic assumptions would both indeed have impacted the calculation of the risk of secondary carcinomas with the different methods, as Roentgen vs. protons. For clinical decision making in favor of or against one used method it is thus sensible to scale the excessive risk of secondary carcinomas compared to the method with the lowest risk rate, proton scanning, and to range the latter method as “risk one”. For results please see Table 4.

As of today's state of science, these figures are the best data the clinician can use for deciding on the radiation therapy method to be used.

### Table 4: Comparison of relative risks of developing a secondary carcinoma

<table>
<thead>
<tr>
<th>Radiation therapy</th>
<th>Proportion of risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional radiation therapy (CRT)</td>
<td>12.4</td>
</tr>
<tr>
<td>Intensity-modulated radiation therapy (IMRT)</td>
<td>7.1</td>
</tr>
<tr>
<td>Proton scattering (PSPT)</td>
<td>1.2</td>
</tr>
<tr>
<td>Proton scanning (IMPT)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 4: Comparison of relative risks of developing a secondary carcinoma with regard to different radiation therapy forms. Up to more than 12-fold increase in risk of developing secondary carcinomas, compared to proton scanning.

### Bibliography:
4. Vogt/Schultz: Grundzüge des praktischen Strahlenschutzes
THE THERAPY

64 OVERVIEW OF TREATMENTS AT RPTC
70 TREATMENT OF CHILDREN AT RPTC
76 RESULTS FROM 500 PATIENTS TREATED WITH PROTON THERAPY FOR PROSTATE CANCER
86 FIRST RESULTS OF PROTON THERAPY FOR PANCREATIC CANCER
92 CASE EXAMPLES FROM RPTC
Even after the fourth operating year, prostate carcinomas are among the most common indications at the RPTC with 500 cases, i.e. 33% of all tumors treated. This is not least because of the high amount of healthy tissue spared, which is possible with protons, and thus the reduced side effects with the same or higher effectiveness. In addition, tumors of the central nervous system (CNS) with 210 cases, a percentage of 14%, account for the second most common group. The precision, which can be reached with protons, as well as the low radiation exposure of healthy tissue are also significant advantages regarding CNS tumors since important nerve structures can be spared better and side effects can thus be reduced. The number of tumors in the thorax area - mainly the lungs - was rising constantly so that this indication accounts also for 13%, i.e. 185 of all cases after the fourth operating year. A strong increase in pancreas carcinomas and extra cranial chordomas and chondrosarcomas could be registered. After 32 pancreas cases towards the end of the third operating year, as many as 52 cases were treated in the fourth operating year alone. This increase by more than 100% reflects the possibilities for pancreas carcinoma treatment with the scanning method of proton therapy. Please see "First Results of Proton Therapy for Pancreatic Cancer". With regard to extra cranial chordomas and chondrosarcomas, the number of cases treated has more than doubled from 29 cases to 59. A local control rate of 100% could be reached for these patients, treated at the RPTC since 2009. The treatment was tolerated very well by all patients; no significant side effects occurred. This corresponds to experience from various studies: In 2009, Ares et. al (Paul Scherrer Institute) published the results of 64 patients that were treated with the spot-scanning proton therapy. After a median follow-up of 38 months a local 5-year-control rate of 81% for chordomas and 95% for chondrosarcomas with minimal toxicity was documented. A report on children and adolescents who were treated with the same method, showed a local control rate of 100% with minimal toxicity as well (Rutz et al, 2008). Compared to proton therapy, the results of a therapy with X-rays are noticeably worse. Zorlu et al (2000)

Figure 1: Overall statistic of indication groups treated at the RPTC until April 2013.

Table 1: Overview of relevant performance parameters as statistic for treatments since RPTC start.
reported a 5-year, progression free survival of only 23%. The results of the chordoma treatments with stereotactic radio surgery are also disappointing: 30-50% local 5-year control rate. The only exception are the results of fractionated stereotactic radio surgery with photons when treating small chondrosarcomas. A local control rate of 100% could be reached.

After operation in the first year started with only one of the four gantries and with 298 patients, more than 1,500 patients from 44 nations have been treated by now. Patients benefit from the currently most modern proton therapy available, the proton scanning. The needle-shaped proton beam works like a paintbrush which fills up the tumor area – like „dot painting“ with colors – spot by spot with the optimal dose. Scattering is minimized with this highly precise positioning of the dose in the tumor. Tumor growth is thus stopped and the surrounding healthy tissue is spared optimally. With more than 1,500 patients treated and 141,423,398 single-dose controlled scanning spots RPTC has gained more experience with this method than any other proton therapy center worldwide (table 1 on page 65 and figure 2). This precision enables us also to ideally irradiate the smallest as well as very large tumors (figure 3).

![Scanning spots per field](chart1)

**Figure 2**: Frequency distribution of number of spots that the tumors treated at the RPTC were divided into (statistic for treatments since RPTC start until April 2013).

![Tumor volumes](chart2)

**Figure 3**: Frequency distribution of tumor volumes of patients treated at the RPTC (statistic for treatments since RPTC start until April 2013).
The number of the individual irradiation sessions depends on the indication and is determined by the therapeutic dose, the dose tolerance of the surrounding tissue and the rate at which cells are regenerating (tumor and healthy cells). The number of fractions applied at the RPTC is based on established treatment protocols from the field of protons and photons; regarding the latter, the dose is converted with the factor 1.1, as common for protons (Figure 4). To spare organs at risk even better the tumor is irradiated from several directions (fields), if necessary (Figure 5).

Table 2: Only a low number of unavailability was registered in 2012. A total availability of 98.1% was thus reached.

<table>
<thead>
<tr>
<th>Availability of the facility in 2012</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned treatment days (incl. days with total unavailability)</td>
<td>275</td>
</tr>
<tr>
<td>Sum of days with total unavailability</td>
<td>3</td>
</tr>
<tr>
<td>Sum of days with partial unavailability pro rata*</td>
<td>2.13</td>
</tr>
<tr>
<td>Availability</td>
<td>98.1%</td>
</tr>
</tbody>
</table>

Table 2: Only a low number of unavailability was registered in 2012. A total availability of 98.1% was thus reached.

Bibliography:

Figure 4: Frequency distribution of number of fractions used at the RPTC (statistic for treatments since RPTC start until April 2013).

Figure 5: Frequency distribution of the number of beam directions (fields) used at the RPTC (statistic for treatments since RPTC start until April 2013).
Since the treatment of children, with the exception of chordomas and low-grade chondrosarcomas of the skull base, at the RPTC and worldwide is performed according to the standards of photon irradiation, with regard to the tumor dose, this tumor dose equals the one in photon irradiation, which results in comparable control rates. Yet proton irradiation spares healthy tissue and critical structures like the brain and hence the intelligence, spinal cord, liver, kidney, lung, etc. verifiably a lot better.

The results of a study on chordomas and low-grade chondrosarcomas of the skull base have already shown that a tumor dose increase, possible with protons, can cause a significant improvement in the cure rate\(^3\)\(^,\)\(^4\)\(^,\)\(^5\). This gives us hope that in the future proton therapy – also concerning further pediatric tumors - will not only reduce acute and late side effects, but will also result in improved cure rates.

The verifiable reduction of side effects and late effects due to a proton therapy for children motivated the German Society for Radio Oncology (Deutsche Gesellschaft für Radioonkologie, DEGRO) as early as 2008 to generally recommend protons instead of photons for the radiation treatment of pediatric tumors.

At the RPTC children with cancer are irradiated according to international protocols with the gentle proton-scanning method. In addition, during therapy concept planning, which often includes further...
aspects aside from the irradiation, and during the treatment itself, RPTC is working closely with the renowned children’s hospital Schwabing, the largest pediatric clinic in Munich.

The proton therapy of infants is performed under anesthesia to prevent the tumor from shifting due to movements. The RPTC has an experienced team of anesthetists for this purpose.

**EXAMPLE: RHABDOMYOSARCOMA**

The 5-year old patient had a rare form of cancer in the left cheek (poorly differentiated embryonic rhabdomyosarcoma). The tumor had infiltrated the left jaw joint, perforated the bone of the skull base and extended to the dura mater (Figure 1).

After the tumor biopsy and diagnosis in June 2010 the patient was treated with chemotherapy from October 2010 to April 2011, according to CWS Guidance. In addition, he was irradiated with protons from February to March 2011. The treatment was very well tolerated by the child.

The aftercare examination in the children’s oncology in Schwabing in December 2011 showed that the tumor was completely reduced in size and that a complete remission had hence been achieved. The only documented aftereffect of proton therapy is a chronic fluid blockage, the collection of fluid in the middle ear. This side effect may result in hearing deficiencies, a feeling of pressure in the ear as well as pain or dizziness.

Compared to a normal radiation therapy, the patient had received a significantly lower dose in the spinal cord due to the special physical characteristics of protons. The oral cavity could be spared better and the opposite side of the face could be kept completely out of the irradiation field.

Altogether the applied overall dose into healthy tissue was significantly lower than with conventional radiation therapy. This could also reduce the risk of secondary tumors after the treatment. Please refer to the comparison between proton irradiation at the RPTC (Figure 2 on page 74) and the theoretical calculation for X-rays (Figure 3 on page 75).

**Bibliography:**


Figure 1: The MRI images from an axial, coronary and sagittal perspective show the spread of the rhabdomyosarcoma of the left cheek prior to the irradiation with protons.
Figure 2: These are the cross sections showing the dose distribution in the irradiation planning for proton treatment at the RPTC. This is how the child patient was irradiated with protons.

Figure 3: Dose distribution in the theoretically calculated comparison with X-rays. This is what the dose distribution with X-rays from five irradiation directions would have looked like. The higher dose burden on healthy tissue, particularly the brain stem, can be clearly seen.
In our third annual report (page 67 et seq.) we tried to provide an overview of the variety of therapy forms offered for prostate cancer: watchful waiting, antihormonal therapy, chemotherapy, surgery, brachytherapy and ultimately external radiotherapy with X-rays or protons. All these therapy forms can, or rather have to be combined two or threefold for advanced cases.

As stated at that time, a health-sociological study in the USA showed disturbing regional differences, from state to state, in the allocation of the therapies offered. For patients it is therefore obviously vital to get involved in gauging therapy effectiveness, the risks and side effects of the different treatment forms. Proton therapy at the RPTC, technically optimized with the scanning method, has the potential to establish itself as superior to further possible radiation therapies. We are therefore reporting annually on the results of our increasing patient numbers and longer follow-up periods. The question is which progress proton therapy will make within the entirety of external radiation therapies. Regarding oncological effectiveness the latter has already proven equal to surgical treatments. Furthermore, radiation therapy is generally free of lethal risks and, has by comparison (in turn with prostatectomy) fewer side effects regarding incontinence and loss of sexual function.

Proton scanning as optimized irradiation form should thus have the potential of combining effective tumor healing with a low number of risks and side effects. This small number of risks and side effects is also an advantage to the so-called “active surveillance” described as well in the previous annual report, which keeps patients free of interventions, but will also burden them with a subjectively felt persistent morbidity and repeated biopsies.

Where is proton scanning going?

PATIENT CHARACTERISTICS

From the start of clinical operation on 16 March 2009 until 2 April 2013 the first 500 patients with prostate cancer were treated at the RPTC. The following evaluation comprises 500 patients. The international RPTC clientele from so far 44 nations characteristically impeded a complete post-therapeutic follow-up: some patients did not hand in all data required. Please see table 1 for detailed patient and tumor characteristics.

Table 1: Patient and tumor characteristics of 500 RPTC patients, which were treated with proton therapy for prostate cancer during the period between 03/09 and 04/13 (evaluable parameters).

### SUMMARY FOR PATIENTS:

The first 500 patients treated with proton scanning for prostate cancer at the RPTC have demonstrated:

- better tolerance,
- fewer side effects,
- therapeutic safety as in high-dose X-ray therapy,
- shorter treatment time and
- well tolerated extension of the irradiation field into the lymph node area for cases with particular risk.
HYPOFRACTIONATED THERAPY
PROCEDURE USED

At the RPTC patients were regularly treated with proton scanning with two opposing fields from the left and right (figure 1). For recurrences and special cases (e. g. hip replacements) different field geometries were used. The therapy consisted regularly of 21 sessions each, five times a week. The standard daily dose was 3.0 Gray RBE (relative biological effectiveness, which takes into account the biological dose-effect ratio of protons compared to X-rays).

The reason why we chose the higher single dose of 3 Gray (RBE) is that the prostate cancer reacts positively to a hypofractionation. This is expressed in the so-called alpha/beta value, which for prostate carcinomas amounts to $\alpha/\beta = 1.5$ Gray, but for long-term complications in the rectum to $\alpha/\beta = 3$ Gray. Due to these differences in fractionation sensitivity, hypofractionation may reduce the side effects and/or increase the tumor control; please see above „How Often Does the Patient Have to Be Irradiated?“. The mild hypofractionation with 21 fractions used at the RPTC is a clear improvement compared to the 41 fractions used in conventional X-ray therapy. The biological effective dose corresponds to a dose of 82 Gray for conventional fractionation.

The field size applied is determined by the risk of an involvement of the pelvic lymph drainage ways (figure 2). This is calculated on the basis of the PSA values, the Gleason scores and the tumor stage. If the risk of a microscopic tumor spread into the pelvic lymph nodes is higher than 15%, an irradiation of the pelvic lymph drainage ways is recommended at

**Figure 1:** The dose distribution in an irradiation plan with protons for a prostate cancer patient treated at the RPTC is shown. The 2 opposing, lateral irradiation directions (fields) from the left and right can be clearly seen.

**Figure 2:** Radiation treatment plan with protons showing dose distribution in a prostate cancer patient at RPTC. Pelvic lymph nodes were included. The 2 opposing, lateral irradiation directions (fields) from the left and right can be clearly seen. Proton scanning enables the simultaneous, targeted irradiation of the lymph node area in both chosen irradiation directions with a deliberately low dose (yellow area).
the RPTC. Therefore, 250 patients (53%) underwent pelvic lymph node irradiation. In this procedure the applied standard dose was 52.5 Gray (RBE) with a fractionation of 21 x 2.5 g Gray (RBE).

TOLERANCE OF PROTON THERAPY
TREATMENT: ACUTE AND CHRONIC SIDE EFFECTS

Acute Side Effects

Side effects during radiation therapy afflict in particular the urinary tract. Only few patients experienced minor side effects of the urinary tract during therapy, like increased urinary urgency and mild burning during urination. Regarding intestinal function, soft stool or an irritation of the rectum was occasionally reported. 5 patients reported stronger side effects of temporary acute retention of urine or very strong urinary urgency. In one case the therapy had to be stopped due to substantial bleeding from the rectum; this patient suffered from a preexisting colitis ulcerosa. Usually, acute toxicity did not last longer than 3-4 weeks and was completely gone 3 months after the end of the proton therapy, see table 2.

Late Toxicity

Late toxicity of radiation therapy occurs months or even years after proton therapy and affects mainly the gastrointestinal or the urinary tract. Late toxicity is classified according to the categories of the Radiation Therapy Oncology Group (RTOG) and divided into minor (Grade 1), moderate (Grade 2), severe (Grade 3) and very severe (Grade 4). Minor toxicities (Grade 1) include slightly increased urinary urgency in the urinary tract and mild diarrhea (maximum 5x/day) and occasionally blood in the stool in the rectum area.

Moderate toxicities (Grade 2) included increased urinary urgency and occasionally blood in the urine in the urinary tract and moderate diarrhea (more than 5x/day), mucous discharge or often blood in the stool in the rectum area.

Severe toxicities (Grade 3) include highly increased urinary urgency or often blood in the urine in the urinary tract and severe bleedings, which require a surgical intervention, or a scar tissue formation, narrowing the intestine in the rectum area.

Very severe toxicities (Grade 4) would be tissue death (necrosis) or fistula formation in the urinary tract and the intestine.

In literature the frequency of moderate toxicities (Grade 2) due to an X-ray irradiation in the urinary and gastrointestinal tract is stated as 7-19%. Severe toxicities (Grade 3) after conventional X-ray therapy account for 5-15% 3, 4, 5, 6.

At the RPTC during the median follow-up period of 9 months, moderate toxicities (according to RTOG classification Grade 2) after proton therapy were seen in only 16 (3.4%) patients: 7 patients experienced increased urinary urgency and required drug treatment. 3 patients had acute urinary retention and needed a short-term urinary diversion or surgical intervention. 6 patients experienced a strong inflammation of the rectum with occasional bleeding, which improved after the administration of local anti-inflammatory suppositories.

Only 3 patients (0.6%) reported severe late toxicities with severe rectum bleeding, which required blood transfusion (table 3). Regarding the urinary tract, no severe late toxicities, according to the RTOG classification, were observed.

Concerning the sexual function, only few patients reported a decrease in erectile function, although many of these patients received an antihormonal therapy, which complicates the causal distinction to proton therapy.

Table 2: Kind and frequency of acute side effects (≥Grade 2, EORTC/RTOG) after proton therapy (n=500).

<table>
<thead>
<tr>
<th>Acute Side Effects</th>
<th>Kind of toxicity</th>
<th>n</th>
<th>Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>During and up to 3 months after completion of proton therapy</td>
<td>Moderate urinary urgency, moderate urinary retention</td>
<td>6</td>
<td>1.2%</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Severe bleeding and discontinuation of therapy due to colitis ulcerosa</td>
<td>1</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Table 3: Kind and frequency of late severe side toxicity (≥Grade 2, EORTC/RTOG) after proton therapy (n=500).

<table>
<thead>
<tr>
<th>Late Toxicity</th>
<th>Kind of toxicity</th>
<th>n</th>
<th>Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 months after completion of proton therapy</td>
<td>Increased urinary urgency</td>
<td>7</td>
<td>1.4%</td>
</tr>
<tr>
<td>Urban retention</td>
<td>4</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>6</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>Bledings from the rectum that require transfusion</td>
<td>3</td>
<td>0.6%</td>
<td></td>
</tr>
</tbody>
</table>
All in all the proton therapy toxicities occurred were noticeably lower than those of conventional X-ray therapy. Of course, these results have to be considered provisionally due to the still relatively short follow-up period, but they confirm our expectations: proton scanning at the RPTC ensures: no surgical lethality, it lowers the danger of a urinary incontinence as well as impotence and causes fewer general complaints compared to a conventional treatment with X-rays, table 3 on page 81.

FIRST RESULTS

The PSA value is an important parameter for treating prostate carcinomas, because it shows the success of the therapy. A PSA reoccurrence is when, according to the definition, the PSA nadir (minimum value) goes up by at least 2ng/ml (RTOG-ASTRO consensus).

To be able to make as early as today a statement regarding a longer follow-up period, a sub-group of 196 patients was evaluated that had been treated from 16 March 2009 (start of clinical operation) to 30 March 2011 at the RPTC. The median follow-up for this group was 21 months. 66 of these patients received a concomitant hormone therapy, 25 of these were post irradiations after prostatectomy. 16 had already distant metastases.

Please see table 4 for detailed patient and tumor characteristics.

The behavior of the prostate-specific antigen (PSA) after proton therapy could be seen in this sub-group in a drop in the median of 7.9 ng/ml to 0.5 ng/ml after definitive (sole) proton therapy; in case of patients with previous prostatectomy a drop of 8.3 ng/ml to 0.1 ng/ml could be registered. Palliative cases are herein included.

During the median follow-up period of 21 months (95% confidence interval 18-23) a PSA recurrence occurred in 13 of the total group (including post and recurrence irradiations) of 196 patients (6.8%), see table 5.

As expected, most recurrences were observed in the high-risk group (n=9). In the low-risk group 2 patients with a PSA recurrence were registered, the same is true for the intermediate-risk group. 95.7% of patients in the low-risk group, 97.4% of patients in the intermediate-risk group and 85.9% of patients in the high-risk group were PSA recurrence free after 21 months.

Please see table 6 for the risk-group definitions.

Comparison with Literature:

A comparison of our first results with published data of conventional radiotherapy is at the moment naturally complicated by the fact that these studies feature vastly longer follow-up periods. Nevertheless, our results correspond to international results. For instance a meta analysis of 5 randomized studies with 1,557 patients (follow-up period of 15 years) resulted in a 5-year survival rate of 94-96% in the low-risk group, of 94% in the intermediate-risk group and of 64-83% in the high-risk group8.

Table 4: Patient and tumor characteristics of 196 RPTC patients, who were treated with proton therapy for prostate cancers during the period between 03/09 and 03/11 (= patient population with median follow-up of 21 months, evaluable parameters).

<table>
<thead>
<tr>
<th>Patient and tumor characteristics</th>
<th>n=196</th>
<th>Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (03/09 to 03/11)</td>
<td>196</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>74</td>
<td>37.7</td>
</tr>
<tr>
<td>T2 and pT2</td>
<td>72</td>
<td>36.7</td>
</tr>
<tr>
<td>T3 and pT3</td>
<td>41</td>
<td>20.9</td>
</tr>
<tr>
<td>T4 and pT4</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>172</td>
<td>87.8</td>
</tr>
<tr>
<td>Positive</td>
<td>20</td>
<td>10.2</td>
</tr>
<tr>
<td>Distant metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>179</td>
<td>91.3</td>
</tr>
<tr>
<td>Positive</td>
<td>16</td>
<td>8.2</td>
</tr>
<tr>
<td>Initial PSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10 ng/ml</td>
<td>115</td>
<td>58.7</td>
</tr>
<tr>
<td>11-20 ng/ml</td>
<td>36</td>
<td>18.4</td>
</tr>
<tr>
<td>&gt; 20 ng/ml</td>
<td>29</td>
<td>14.8</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-6</td>
<td>73</td>
<td>37.2</td>
</tr>
<tr>
<td>7</td>
<td>81</td>
<td>41.3</td>
</tr>
<tr>
<td>8-10</td>
<td>35</td>
<td>17.9</td>
</tr>
<tr>
<td>Risk group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>46</td>
<td>23.5</td>
</tr>
<tr>
<td>Intermediate</td>
<td>78</td>
<td>39.8</td>
</tr>
<tr>
<td>High</td>
<td>64</td>
<td>32.7</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>66</td>
<td>33.7</td>
</tr>
<tr>
<td>No</td>
<td>125</td>
<td>63.8</td>
</tr>
<tr>
<td>Prostatectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25</td>
<td>12.8</td>
</tr>
<tr>
<td>No</td>
<td>171</td>
<td>87.2</td>
</tr>
<tr>
<td>Previous irradiation treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>No</td>
<td>194</td>
<td>99.0</td>
</tr>
</tbody>
</table>

Table 5: PSA recurrence after proton therapy, depending on risk group (n=196, median follow-up 21 months, evaluable 188).

<table>
<thead>
<tr>
<th>PSA recurrence after proton therapy</th>
<th>Low risk n=46</th>
<th>Intermediate risk n=78</th>
<th>High risk n=64</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA recurrence</td>
<td>2</td>
<td>4.3%</td>
<td>2</td>
</tr>
<tr>
<td>No PSA recurrence</td>
<td>44</td>
<td>95.7%</td>
<td>76</td>
</tr>
</tbody>
</table>

[^8]: Based on a meta-analysis of 5 randomized studies with 1,557 patients, published in 2013.
DIRECTIONS OF DEVELOPMENT FOR PROTON SCANNING FOR PROSTATE CARCINOMAS

The increasing establishment of our procedure allows for a reduction of the follow-up failures in foreign patients – an improving trend can already be seen.

The additional irradiation of pelvic lymph nodes for the lower risk groups as well is not performed according to valid standards of conventional radiation therapy, since the side effects on the intestine will exceed the positive effect there. With the targeted irradiation with protons these can, however, be reduced, so that the irradiation of the lymph drainage ways can mean a further advantage for our patients. Already now we are thus recommending a routine irradiation of the lymph drainage ways in the high and intermediate risk groups. In the future we will discuss a standardized extension of the irradiation field along the lymph node sites for low-risk patients as well.

For some years a change in the fractionation for the external X-ray irradiation of prostate carcinomas has been discussed. By now the results from several phase II studies are available, in which patients were treated with only 5 fractions and overall doses of 35 to 37 Gray. Since the targeting precision of proton scanning leads to a lower radiation dose in healthy tissue by an only limited anatomy-dependent factor of approx. 3-5, our aim is to use the internationally analyzed hypofractionation regime, currently used in conventional prostate irradiation, with only five irradiation sessions as well. Due to the favorable alpha/beta ratio of only 1.5 Gray in prostate carcinomas, this hypofractionation seems to result in a high effective does at the tumor, which allows for a reduction of the physical dose to only 35 Gray.

### Prognostic factors of prostate cancer

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA value</td>
<td>≤10 ng/ml</td>
<td>11-20 ng/ml</td>
</tr>
<tr>
<td>Gleason score</td>
<td>Max. 6</td>
<td>7</td>
</tr>
<tr>
<td>Tumor stage</td>
<td>cT1c or cT2a</td>
<td>cT2b</td>
</tr>
</tbody>
</table>

Table 6: Prognostic factors of prostate cancer.

Bibliography:

The combination of radiation therapy and chemotherapy may be better than a monotherapy. A combination, however, will result in higher toxicities over the course of treatment. Radiotherapy with its meanwhile modern technologies is hence in high demand. Safety margins have to be narrowed down, overall doses have to be raised, healthy tissue like myelon, kidneys, liver, small intestine and stomach have to be protected optimally.

The questions about the right point in time for radiotherapy (concomitant vs. sequential), which chemotherapy and with which dosage, overall dose of radiotherapy, the definition of the irradiation field as well as the standing of proton therapy remain unanswered.

Indication Proton Therapy:
The rationale for the clinical application of protons in the treatment regime was given as early as 1946 by Dr. Robert Wilson. Wilson outlined that protons emit only very little energy on their way to a predefined target, most of their energy is given off in the target (Bragg peak) and no ionization will occur behind the target, at the end of the pathway. By now thousands of patients with different forms of cancer have been treated effectively and safely with protons. The list of indications is expanding constantly and thus also the corresponding verified literature.

A corresponding indication for pancreas carcinomas is valid in the following situations:
1. Definitive proton therapy for locally advanced inoperable carcinomas
2. Proton therapy in neoadjuvant setting
3. Proton therapy adjuvant in R1 situation
4. Proton therapy for local recurrence after operation

The radiation therapy should be combined with a systemic therapy in the form of chemotherapy or targeted therapy if the patient fulfills the relevant preconditions.

The following indications have to be clarified in studies:
1. Proton therapy for R0 resection but safety margin < 1mm
2. Proton therapy for local recurrence after previous irradiation

Basis for Treatment Concepts with Protons:
As early as 2005 Wilkowski et al. demonstrated in a meta analysis that a dose increase in radiation therapy or chemotherapy or in both will lead to significantly better response to therapy. Up to 1/3 of the patients classified as inoperable could be operated successfully after this therapy. The success, however, had to be paid with a noticeable rise in the number of unacceptable toxicities.

The average survival period of untreated patients with pancreas carcinomas is 3 months, while the survival rate after radical operations lies between 10 and 20 months. All in all, a 5-year survival rate of approximately 3-4% can be assumed. Patients with tumors that are confined to the pancreas and have a diameter of less than 3 cm have a better prognosis than those with larger tumors or an infiltration of the retroperitoneum. Patients with R0 resection have the most favorable prognosis.

The aim of a pre-surgical/neoadjuvant radiotherapy for pancreatic cancer that is principally classified as resectable is to improve resectability by diminishing the tumor, the potential avoidance of intra-surgical spreading of tumor cells, an earlier therapy of the systemic disease and a possibly higher resectability rate than with the post-surgical/adjuvant therapy. Associated with these potential advantages is the improvement of the recurrence free survival and overall survival.

In principle it can be assumed that, in case of a neoadjuvant radiotherapy, more favorable biological conditions (unchanged vascularization, oxygen saturation) can be found in the tumor that lead to a better response to radiation therapy in particular, but also to chemotherapy.

In case of a locally advanced inoperable pancreas carcinoma the available literature provides conflicting results and there is no clear standard for therapeutic procedure. The combination of radiation therapy and chemotherapy may be better than a monotherapy. A combination, however, will result in higher toxicities over the course of treatment. Radiotherapy with its meanwhile modern technologies is hence in high demand. Safety margins have to be narrowed down, overall doses have to be raised, healthy tissue like myelon, kidneys, liver, small intestine and stomach have to be protected optimally.

The questions about the right point in time for radiotherapy (concomitant vs. sequential), which chemotherapy and with which dosage, overall dose of radiotherapy, the definition of the irradiation field as well as the standing of proton therapy remain unanswered.

Indication Proton Therapy:
The rationale for the clinical application of protons in the treatment regime was given as early as 1946 by Dr. Robert Wilson. Wilson outlined that protons emit only very little energy on their way to a predefined target, most of their energy is given off in the target (Bragg peak) and no ionization will occur behind the target, at the end of the pathway. By now thousands of patients with different forms of cancer have been treated effectively and safely with protons. The list of indications is expanding constantly and thus also the corresponding verified literature.

A corresponding indication for pancreas carcinomas is valid in the following situations:
1. Definitive proton therapy for locally advanced inoperable carcinomas
2. Proton therapy in neoadjuvant setting
3. Proton therapy adjuvant in R1 situation
4. Proton therapy for local recurrence after operation

The radiation therapy should be combined with a systemic therapy in the form of chemotherapy or targeted therapy if the patient fulfills the relevant preconditions.

The following indications have to be clarified in studies:
1. Proton therapy for R0 resection but safety margin < 1mm
2. Proton therapy for local recurrence after previous irradiation

Basis for Treatment Concepts with Protons:
As early as 2005 Wilkowski et al. demonstrated in a meta analysis that a dose increase in radiation therapy or chemotherapy or in both will lead to significantly better response to therapy. Up to 1/3 of the patients classified as inoperable could be operated successfully after this therapy. The success, however, had to be paid with a noticeable rise in the number of unacceptable toxicities.
Ben-Josef et al. showed in 2008 that an intensification of therapy resulted in a better local control, a better progression free survival as well as a better overall survival. Yet the success in this case was also disparaged due to unacceptable side effects.

In 2007 Kozak et al. proved quite impressively that by using protons in the treatment concept for pancreas carcinomas, a dose increase and hypofractionation can be applied safely and effectively without raising toxicity. This dosimetric study demonstrated that the radiation burden on organs at risk is significantly lower compared to the conventional radiation therapy with photons.

Due to the physical characteristics of protons the desired higher dose in the tumor can thus be achieved with homogenous dose utilization while sparing the healthy tissue optimally.

**TREATMENT AT RINECKER PROTON THERAPY CENTER:**

From summer 2009 to January 2013 a total of 84 patients with inoperable, histologically confirmed pancreas carcinomas were irradiated. 49 patients that fulfilled the relevant criteria were included in an internal protocol and evaluated correspondingly. The other 35 patients were treated according to individual protocols or have not yet reached the first aftercare examination.

36 patients (73%) received 18 x 3 Gray (RBE) in the primary tumor region, 6 patients (12%) were irradiated with 10 x 4 Gray (RBE) in the primary tumor and with 3 x 14 Gray (RBE) at the liver metastases; a further 2 patients (4%) received in addition to 10 x 4 Gray (RBE) in the primary tumor 3 x 12.5 Gray (RBE) in the area of the liver metastases. Another patient (2%) was irradiated with 10 x 4 Gray (RBE) at the primary tumor and with 10 x 3.5 Gray (RBE) in the area of the loco regional lymph drainage ways. Each patient (thus 4%) was irradiated with 18 x 3 Gray (RBE) at the primary tumor and with 1 x 22 Gray (RBE) or 5 x 8 Gray (RBE) in the area of the liver metastases; 1 patient (2%) received 10 x 4 Gray (RBE) in the primary tumor, 10 x 3.5 Gray (RBE) in the area of the loco regional lymph drainage ways and 4 x 10 Gray (RBE) in the area of the liver metastases. For only 1 patient (2%) the dose in the primary tumor had to be reduced to 15 x 3 Gray (RBE) due to side effects of chemotheraphy.

26 (53%) patients received concomitantly chemotheraphy with gemcitabine 300 mg/m² per week.

For patients with 10 fractions in the primary tumor and concomitant irradiation of the liver metastases, the therapy was given under anesthesia (apnea) to avoid shifting of the tumor due to respiratory movement.

Initially, all patients underwent a staging with MRT abdomen and PET/CT; prior to the therapy the liver function parameters were documented; the therapy itself was given under image control and highly precise patient positioning.

Please see table 1 for an overview on patient population.

### Patient population

<table>
<thead>
<tr>
<th>Age</th>
<th>N = 49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>58.5 years</td>
</tr>
<tr>
<td>Range</td>
<td>40-82 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>33 (67%)</td>
</tr>
<tr>
<td>Male</td>
<td>16 (33%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target area irradiated</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary pancreatic tumor</td>
<td>28 (57%)</td>
</tr>
<tr>
<td>Primary pancreatic tumor and lymph drainage ways</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Primary pancreatic tumor and metastases</td>
<td>12 (25%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proton dose</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>18 x 3 Gy (RBE)</td>
<td>36 (73%)</td>
</tr>
<tr>
<td>15 x 3 Gy (RBE)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>10 x 4 Gy (RBE) + Stereotactic proton therapy for metastases and simultaneous hypofractionated proton therapy of regional lymph drainage ways.</td>
<td>12 (25%)</td>
</tr>
</tbody>
</table>

RESULTS:

**Toxicity**

Acute toxicity and side effects during follow-up are classified according to RTOG/EORTC criteria and summarized in table 2 on page 90. The median follow-up is at 7.5 months.

A hypofractionated proton therapy with the scanning procedure and application of an effective tumor dose can be given safely and tolerably. Regarding the patients treated so far, no therapy-induced termination of treatment due to undesired events has occurred. During the therapy and up to 28 months later no Grade 3 or Grade 4 toxicities were registered. A patient (2%) experienced a Grade 1 radio dermatitis; 14 patients (29%) reported Grade 1 nausea and lack of appetite, 5 patients Grade 2 (10%), which was rather caused by chemotherapy. 30 patients (61%) completed the irradiation in a good general condition without therapy-relevant toxicity. So far 3 months after the end of therapy only one Grade 2 side effect (2%) has been documented. No late complications in the area of the organs at risk as spinal cord, kidneys, liver, duodenum and stomach have been documented; by means of monitoring the blood counts no severe complications due to a compression of the bile duct were observed.

Please see table 2 for toxicities.
Local Control

Of all the 45 patients already in follow-up a reduction in tumor size was achieved. These results were image-based evaluated with MRT and PET/CT three months after completion of the therapy. 6 months after the end of therapy a complete local control could be documented for the 22 patients already registered. 18 patients (45%) have not yet been to the 6-month control. See table 3 for local control.

Overall Survival

A follow-up examination one year after proton therapy was already conducted for 9 patients. The local control, however, has been achieved on all image-based controlled patients. Yet 14 patients died during this period of time, 1 patient from an MRSA infection during the adjuvant chemotherapy. 12 patients died from metastasis unknown or not yet apparent during the therapy. 1 patient died from an intestinal ileus without recognizable reference to radiation therapy. Two patients were lost in follow-up.

SUMMARY:

Proton therapy enables homogenous dose distribution and a high overall dose within the tumor with a noticeably low dose exposure to the corresponding organs at risk. In comparison with conventional photon therapy, proton therapy allows a significantly better protection of these risk structures, which clinically correspond to low toxicities. Therefore, hypofractionated high-dose proton therapy is safe and effective and should be offered in combination with chemotherapy for patients with locally advanced pancreatic cancer.

We are currently preparing prospective study protocols to optimize the overall dose. Moreover, the optimal concurrent and adjuvant chemotherapy has to be defined.

Bibliography:


Local control

<table>
<thead>
<tr>
<th>Local tumor control 3 months after proton therapy (n=46)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 patients (98%)</td>
<td>100%</td>
</tr>
<tr>
<td>1 patient (2%)</td>
<td>Not yet in 3 month control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Local tumor control 6 months after proton therapy (n=40)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 patients (55%)</td>
<td>100%</td>
</tr>
<tr>
<td>18 patients (45%)</td>
<td>Not yet in 6 month control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Local tumor control 12 months after proton therapy (n=35)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 patients (26%)</td>
<td>100%</td>
</tr>
<tr>
<td>26 patients (74%)</td>
<td>Not yet in 12 month control</td>
</tr>
</tbody>
</table>

Table 2: Evaluated patient population – results side effects, documented side effects during and up to 6 months after the therapy

<table>
<thead>
<tr>
<th>Local Control 3 months after completion of proton therapy (n=46)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 patients (98%)</td>
<td>100%</td>
</tr>
<tr>
<td>1 patient (2%)</td>
<td>Not yet in 3 month control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Local Control 6 months after completion of proton therapy (n=40)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 patients (55%)</td>
<td>100%</td>
</tr>
<tr>
<td>18 patients (45%)</td>
<td>Not yet in 6 month control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Local Control 12 months after completion of proton therapy (n=35)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 patients (26%)</td>
<td>100%</td>
</tr>
<tr>
<td>26 patients (74%)</td>
<td>Not yet in 12 month control</td>
</tr>
</tbody>
</table>

Table 3: Evaluated patient population – results of local control
CASE EXAMPLE: ATYPICAL MENINGEOMA

After conventional radiation the tumor recurred. Due to the tumor localization surgery was not an option. Because of the previous radiation exposure to the brainstem, it was not possible to apply further irradiation therapy with photons.

With protons an effective dose could again be brought into the tumor while the brainstem was spared optimally.
CASE EXAMPLE:
PEDIATRIC EMBRYONIC RHABDOMYOSARCOMA

In case of a treatment with photons, the contralateral oral cavity would also have been exposed to radiation.

The inner ear and the spinal cord were exposed to a noticeably lower dose with protons when compared with photons. Furthermore, bones and contralateral oral cavity were protected. To keep the risk of secondary tumors as low as possible, children should be irradiated with protons, according to the guidelines of the German society for radiation oncology (Deutsche Gesellschaft für Radio-Onkologie, DEGRO).

Theoretically calculated comparison

<table>
<thead>
<tr>
<th>Tissues</th>
<th>GTV1</th>
<th>PTV1</th>
<th>PTV2</th>
<th>Brainstem</th>
<th>Eye left</th>
<th>Myelon</th>
<th>Lense left</th>
<th>Chiasm</th>
<th>Optic nerve left</th>
<th>Jaw joint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose range (%)</td>
<td>100%</td>
<td>95-100%</td>
<td>90-95%</td>
<td>80-90%</td>
<td>60-80%</td>
<td>40-60%</td>
<td>20-40%</td>
<td>10-20%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PROTONS
As irradiated at RPTC

<table>
<thead>
<tr>
<th>Tissues</th>
<th>GTV1</th>
<th>PTV1</th>
<th>PTV2</th>
<th>Brainstem</th>
<th>Eye left</th>
<th>Myelon</th>
<th>Lense left</th>
<th>Chiasm</th>
<th>Optic nerve left</th>
<th>Jaw joint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose range (Gy)</td>
<td>0.00</td>
<td>20.00</td>
<td>40.00</td>
<td>60.00</td>
<td>80.00</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose range (%)</td>
<td>100%</td>
<td>95-100%</td>
<td>90-95%</td>
<td>80-90%</td>
<td>60-80%</td>
<td>40-60%</td>
<td>20-40%</td>
<td>10-20%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patient: Age 5, male
Diagnose: Embryonic Rhabdomyosarcoma (< 5 cm) of left cheek with infiltration of left temporomandibular joint, skull base and close contact to the meninges
Course of therapy:
06/10 Tumor biopsy and diagnosis
10/10-04/11 Chemotherapy according to CWs – guidance
02/11-03/11 Proton therapy according to CWs-protocol
05/11-10/11 Sustaining chemotherapy according to CWs – guidance
Proton dose: 28 x 1.8 Gy (RBE) to 50.4 Gy (RBE)
Side effects: Labyrinthitis that was healed within a few weeks after the end of PT
Current status: 12/12 Children’s oncology Schwabing, Munich:
- No evidence of remaining tumor or local recurrence
- Complete remission

Patient: Age 5, male
Diagnose: Embryonic Rhabdomyosarcoma (< 5 cm) of left cheek with infiltration of left temporomandibular joint, skull base and close contact to the meninges
Course of therapy:
06/10 Tumor biopsy and diagnosis
10/10-04/11 Chemotherapy according to CWs – guidance
02/11-03/11 Proton therapy according to CWs-protocol
05/11-10/11 Sustaining chemotherapy according to CWs – guidance
Proton dose: 28 x 1.8 Gy (RBE) to 50.4 Gy (RBE)
Side effects: Labyrinthitis that was healed within a few weeks after the end of PT
Current status: 12/12 Children’s oncology Schwabing, Munich:
- No evidence of remaining tumor or local recurrence
- Complete remission

MRI prior to proton therapy
MRI after proton therapy: Complete remission

MRI prior to proton therapy
MRI after proton therapy: Complete remission
The local recurrence had already been exposed to an X-ray dose of 66 Gy; a further irradiation with photons would not have been possible due to the exposure of the surrounding healthy lung tissue as well as the closely-located spinal cord.

With protons re-irradiation with the necessarily high dose is possible. Spinal cord and lung could be protected optimally. The opposite lung was not exposed to any radiation.
CASE EXAMPLE: LUNG METASTASES

Irradiation of a single pulmonary metastasis. Owing to the special delivery method with apnea and protons, it is possible to keep the uncertainty mesh as small as possible, and to spare the healthy lung tissue optimally. Compared with conventional photon therapy, the dose in the healthy tissue is noticeably lower.

**Patient**
Age 62, male

**Diagnose**
Renal cell carcinoma, initial diagnosis 10/2007

**Course of therapy**
- 10/07 Tumor nephrectomy
- 06/08 Start chemotherapy (sutent) for mediastinal lymph node metastases
- 08/10 Irradiation of mediastinal lymph nodes with photons due to progress
- 10/12 Proton therapy of a progressive lung metastasis

**Proton dose**
3 x 14 Gy (RBE) to 42 Gy (RBE) in functional apnea

**Side effects**
No side effects documented

**Current status**
Check-up scheduled for end of March 2013
CASE EXAMPLE:
CARCINOMA OF THE PANCREATIC HEAD

A high-dose irradiation with X-rays would not have been feasible due to the organs at risk surrounding the pancreas and thus the carcinoma (intestine, kidney, spinal cord).

---

**Patient**
Age 53, female

**Diagnose**
Carcinoma of the pancreatic head 10/2011
pT3 N1 M0 R0

**Course of therapy**
10/2011 Duodenopancreatectomy with adjuvant gemcitabine
11/2012 Local unresectable recurrent tumor
12/2012 Proton therapy

**Proton dose**
PTV: 10 x 4 Gy (RBE) to 40 Gy (RBE) in functional apnea
GTV: 10 x 4.4 Gy (RBE) to 44 Gy (RBE) integrated boost

**Side effects**
No side effect associated with therapy

**Current status**
Follow-up ongoing

---

**Dose range**

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 105 %</td>
<td>0.00</td>
</tr>
<tr>
<td>100-105 %</td>
<td>10.00</td>
</tr>
<tr>
<td>95-100 %</td>
<td>20.00</td>
</tr>
<tr>
<td>90-95 %</td>
<td>30.00</td>
</tr>
<tr>
<td>80-90 %</td>
<td>40.00</td>
</tr>
<tr>
<td>70-80 %</td>
<td>50.00</td>
</tr>
<tr>
<td>50-70 %</td>
<td>60.00</td>
</tr>
<tr>
<td>30-50 %</td>
<td>70.00</td>
</tr>
<tr>
<td>10-30 %</td>
<td>80.00</td>
</tr>
</tbody>
</table>

**Tissues**
- GTV
- PTV
- Kidney left
- Myelon
- Intestine
- Intestine I

---

**X-RAYS**

Theoretically calculated comparison

---

**PROTONS**

As irradiated at RPTC

---

9 fields IMRT
1 field proton scanning
CASE EXAMPLE:
PEDIATRIC SYNOVIAL SARCOMA

For an irradiation with photons the right ovary would have had to be relocated surgically to enable perseveration of the function.

With the use of protons the opposite ovary could be spared. The surgical intervention could be avoided.
CASE EXAMPLE: PROSTATE CANCER

With the isolated proton irradiation of the prostate the exposure of the organs at risk (rectum and bladder) could be significantly reduced, compared to the irradiation with IMRT X-rays. In this way a significant reduction in acute as well as late toxicity can be expected.

Patient: Age 59, male  
Diagnose: Prostate carcinoma ED 08/2011  
PbT1cN0cM0 Gleason Score 3 + 3 = 6  
PSA 11 ng/ml  
Course of therapy: 08/2011 Biopsy confirmation  
Proton dose: 1/2011 Proton therapy of the prostate and seminal vesicles  
Side effects: No side effects associated with therapy  
Current status: 02/2012 PSA 3.36 ng/ml  
08/2012 PSA 0.88 ng/ml
CASE EXAMPLE:
PROSTATE CANCER WITH INCLUSION OF PELVIC LYMPH DRAINAGE WAYS

With proton irradiation of the prostate and lymph drainage ways the rectum and urinary bladder could be spared better. In addition, during the irradiation of the lymph drainage ways the intestine could be spared; no further toxicity although the target volume is high.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age 73, male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnose</td>
<td>Prostate carcinoma ED 02/2012</td>
</tr>
<tr>
<td>pT2c cNO cMO  Gleason Score 3+4 = 7a  iPSA 19.01 ng/ml</td>
<td></td>
</tr>
<tr>
<td>Course of therapy</td>
<td>02/12  Biopsy confirmation</td>
</tr>
<tr>
<td>07/12  Proton therapy: prostate and seminal vesicles as well as regional pelvic lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>Pollakisuria Grade I, dysuria Grade I</td>
</tr>
<tr>
<td>Lymph drainage ways: 21 x 2.5 Gv (RBE) to 52.5 Gv (RBE)</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>No therapy-associated side effects during duration of treatment</td>
</tr>
<tr>
<td>Current status</td>
<td>10/12  PSA 0.44 ng/ml</td>
</tr>
<tr>
<td>01/13  PSA 0.14 ng/ml</td>
<td></td>
</tr>
</tbody>
</table>

---

**Dose range**
- 100 %
- 95-100 %
- 90-95 %
- 80-90 %
- 60-80 %
- 40-60 %
- 20-40 %
- 10-20 %

**Tissues**
- GTv1
- PTV1
- CTv1
- CTv2
- Rectum

---

**X-RAYS**
Theoretically calculated comparison

---

**PROTONS**
As irradiated at RPTC

---

**9 fields IMRT**

---

**2 fields proton scanning**
CASE EXAMPLE:
METASTASES OF PROSTATE CANCER

Due to high precision and sharp dose gradients of proton therapy the para-aortic lymph node metastases could be irradiated with a high dose despite a prior photon exposure of prostate and lymph nodes in pelvic area.

Patient
Age: 64, male
Diagnose
Prostate carcinoma ED 08/2011 pT3b pN1 cMO Gleason Score 5 + 4 = 9 iPSA 4.9 ng/ml
Course of therapy
08/11 Radical prostatectomy and lymphadenectomy
11/11 Consolidating radiotherapy (photons) 33 x 2 Gy to 66 Gy including iliac lymph drainage ways
08/12 Para-aortic lymph node recurrence, PSA 2.15 ng/ml
09/12 Proton therapy para-aortic lymph drainage ways with integrated boost for PET-positive lymph nodes
Proton dose
Lymph drainage ways: 21 x 2.5 Gy (RBE) to 52.5 Gy (RBE)
Boost: 21 x 3.0 Gy (RBE) to 63.0 Gy (RBE)
Side effect
No therapy-associated side effects
Current status
01/13 PSA 0.5 ng/ml (during antihormone therapy)
Imaging metastasis right hip & 2 metastases rips, corresponding pain symptoms
03/13 Proton therapy of osseous metastases
Proton dose
Metastases rips (close to spine): 10 x 4.0 Gy (RBE) to 40.0 Gy (RBE)
Metastasis right hip: 10 x 3.0 Gy (RBE) to 30.0 Gy (RBE)

Dose range
- > 115 %
- 100-115 %
- 95-100 %
- 90-95 %
- 80-90 %
- 70-80 %
- 60-70 %
- 50-60 %
- 40-50 %
- 30-40 %
- 20-30 %
- 10-20 %

Tissues
- PTV1
- PTV4
- PTV5
- PTV6
- PTV7
- Kidney left
- Kidney right
- Myelon

Dose range
- > 115 %
- 100-115 %
- 95-100 %
- 90-95 %
- 80-90 %
- 70-80 %
- 60-70 %
- 50-60 %
- 40-50 %
- 30-40 %
- 20-30 %
- 10-20 %

Tissues
- PTV1
- PTV4
- PTV5
- PTV6
- PTV7
- Kidney left
- Kidney right
- Myelon

Due to high precision and sharp dose gradients of proton therapy the para-aortic lymph node metastases could be irradiated with a high dose despite a prior photon exposure of prostate and lymph nodes in pelvic area.
RINECKER PROTON THERAPY CENTER (RPTC)

Telephone: +49 (0) 89 660 680
E-mail: patient@rptc.de
Internet: www.rptc.de
Address: Schäftlarnstrasse 133, 81371 München, Germany