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From Röntgen Rays to Carbon Ion Therapy: The Evolution of Modern Radiation Oncology in Germany

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Introduction

Beginning with the discovery of X rays in 1895, German scientists and clinicians were instrumental in establishing the fields of diagnostic and therapeutic radiology, creating the first radiation therapy peer-reviewed journal, and holding the first international oncologic conference. These landmark achievements profoundly influenced the nascent field of radiation oncology. However, the rapid early scientific progress was halted by World War I, derailed during World War II, and slowly reestablished amid the divisions of the Cold War. Figure 1 chronicles many radiation therapy milestones during these distinct periods. Today, Germany has reemerged as a scientific leader in the field of radiation therapy and a pioneer in radiobiology research and clinical implementation of particle therapy. Here we explore the technical advances and the clinical evolution of radiation therapy in Germany from the groundbreaking establishment of Bismarck's health care system to a modern view of radiation therapy practice.

Establishment of the Bismarck Health Care System

Otto von Bismarck, born in Schönhausen of modern-day Saxony-Anhalt in 1815, is considered the father of many contemporary health care systems, including in his native Germany (1). Perhaps best known for his political philosophy *Realpolitik*, a pragmatic political system based on the reality of circumstances rather than any specific ideology, he held a pivotal role in the German unification of 1871, which required the navigation of frequently harrowing political waters. On one hand, Bismarck was beholden to the Prussian aristocracy, to whom he owed his position as chancellor of the newly formed empire. On the other, the socialist movement and liberal ideology of the time were rapidly gaining influence in the mid-19th century during which time Bismarck's Prussian contemporary, Karl Marx, wrote *Manifest der kommunistischen Partei* and *Das Kapital*. Bismarck's famed political strategy, including his health care agenda, required the implementation of legislation that would satisfy diametrically opposed forces (2).

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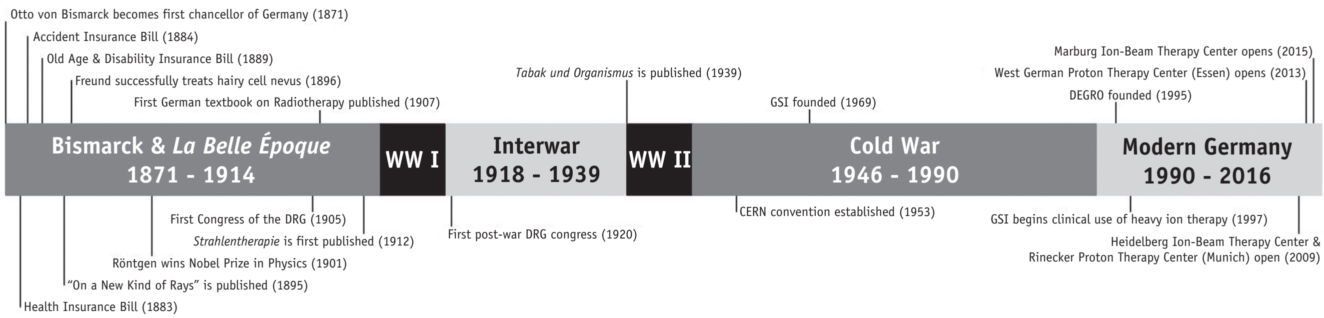

Fig. 1. Timeline of radiation therapy milestones in Germany.

On November 17, 1881, Bismarck urged the Reichstag to adopt a program of *Staatssozialismus*, or state socialism. The German legislature responded with the introduction of three bills while Bismarck remained in power: the health insurance bill of 1883, the accident insurance bill of 1884, and the old age and disability insurance bill of 1889. Whereas further welfare state projects would be implemented following Bismarck's fall from grace, these bills represent the first major global foray into a regulated health care system.

The Bismarck model, persisting 133 years since its introduction, has evolved within its homeland and has been propagated internationally. The Bismarck model mandates universal health care through the creation of "sickness funds"—essentially insurance policies funded jointly by employer and employee. This model is unchanged at its core today and represents the backbone with which modern oncologic care is delivered in Germany. Its European rival is the Beveridge model, a single-payer universal health care system named after William Beveridge, the father of the United Kingdom's National Health Services (3).

Wilhelm Conrad Röntgen's Discovery of X Rays

In the 19th century, Germany was not merely an incubator for social policy, which still dominates today's medical practice, but was also at the forefront of scientific discovery. In late fall of 1895 at the University of Würzburg, Wilhelm Conrad Röntgen unknowingly released X rays from cathode ray tubes (4). These X rays struck nearby paper coated with barium platinocyanide, causing it to "light up with brilliant fluorescence" (5, 6). Röntgen hastily published his finding in an article titled *"Über eine neue Art von Strahlen"* ("On a New Kind of Ray") in the journal of the Würzburg Physical-Medical Society on December 28, 1895 (Fig. 2) (7). Röntgen's wife, Anna Bertha Ludwig, when shown the now iconic X ray image of her hand, famously remarked, "I have seen my own death!" The image would be presented at a meeting of the Berlin Physical Society a week later in January, the first public display of the medical X ray. News of his discovery, which due to of their peculiarity he named X rays "for the sake of brevity," propagated widely throughout the industrial world, culminating with a *New York Times* article on January 12, 1896 proclaiming "Hidden Solids Revealed!" (8).

A wildly productive period in the novel field of radiation physics followed, with the discovery of radioactivity by Henri Becquerel in France in 1896 and the electron by J. J. Thompson in England in 1897 (6). Although there is some controversy regarding the first therapeutic use of X rays, the successful treatment in Vienna of a giant hairy cell nevus by Leopold Freund in November 1886 is one of the first documented in the literature (9). Emerging evidence suggest that in the French city of Lyon the first oncologic application of


EINE NEUE ART

VON

STRAHLEN.

VON

DR. W. RÖNTGEN,

O. Ö. PROFESSOR AN DER K. UNIVERSITÄT WÜRZBURG.

WÜRZBURG.

VERLAG UND DRUCK DER STAHEL'SCHEN K. HOF- UND UNIVERSITÄTS-BUCH- UND KUNSTHANDLUNG.

Ende 1895.

60 ₰.

Fig. 2. "On a New Kind of Ray," journal of the Würzburg Physical-Medical Society, December 28, 1895.

radiation was performed by Victor Despeignes, who treated a neighbor with what was likely gastric lymphoma in July 1896 (10). In the *Lyon Medical Journal*, Despeignes detailed a vivid description of this patient's remarkable clinical response, concluding, "…dealing with a less advanced and less rapid cancerous affliction, we might not have the hope, if not of a cure, at least, of a prolonged survival by using the treatment that we have inaugurated." Oncologic applications were far from the only pursuits, inasmuch as explorations into therapeutic radiation were wide-ranging and were adopted enthusiastically, including in the treatment of tuberculosis.

The early years of the 20th century were remarkably productive, punctuated by the founding of the *Deutsche Röntgengesellschaft* (German Röntgen Society, DRG) in 1905 and the founding of the *Institut für Experimentelle Krebsforschung* (Institute for Experimental Cancer Research) in 1906, a predecessor of the modern *Deutsches Krebsforschungszentrum* (German Cancer Research Center) (11). The Institute for Experimental Cancer Research founder was Vincenz Czerny, a professor of surgery and a pioneer in multidisciplinary oncologic treatment (Fig. 3). Contributions from multiple German natives helped propel the nascent field internationally with the publication of the first German radiation therapy textbook in 1907 and the world's first radiation oncology journal, *Strahlentherapie*, published in 1912. Figure 4A illustrates a typical radiation therapy treatment room in Heidelberg, circa 1912, and is juxtaposed with a modern treatment room at the Heidelberg Ion Beam Therapy Center (Fig. 4B). In the prewar era, Germany not only was responsible for critical developments in radiology and radiation therapy but was a driving force in the international cancer research community.

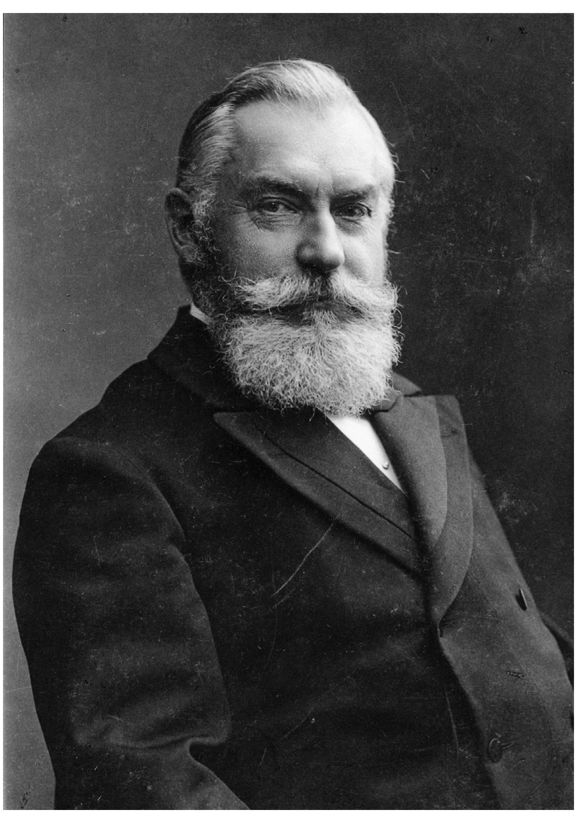

Fig. 3. Vinzenz Czerny (1842-1916) surgeon and founder of the Institute for Experimental Cancer Research.

Turbulence and Tragedy of World Wars I and II

The tremendous scientific leaps observed during *La Belle Époque*—a period of Western European prosperity between 1871 and 1914 that produced many technical and cultural innovations—came to an abrupt halt in Germany on June 28, 1914 when the assassination of Archduke Franz Ferdinand ushered in the Great War and effectively severed German radiologists from the international scientific community. During World War I, all DRG congresses ceased. With the exception of a few scattered radiologic publications, very little is known about radiologic research during this period, and no DRG archives exist. The first postwar DRG congress occurred in 1920, and fierce debate revolved around the establishment of radiology as an independent specialty or fragmentation of the specialty into specific wings within surgery and internal medicine (11). This debate would rage on for several more decades despite radiology's independence elsewhere in Europe and the United States, prompting the Swiss radiologist Hans Schinz of the Röntgeninstitut of the University of Zürich to remark, "Germany, Röntgen's homeland, has curiously dropped behind." At the same time, questions began to arise regarding the fundamental concept of fractionation. The German school of thought was to deliver massive toxic doses of radiation over a minimal number of treatment fractions, but morbid late effects and poor tumor control led to unease in the radiology community, and the French model of fractionation would ultimately spread throughout Europe (4).

The early 1930s heralded a tumultuous and tragic era with the rise of the Nazi regime. The insidious infiltration of the Nazi state into the scientific community, termed *Gleichschaltung*, or Nazification, resulted in the neutralization of political dissidents by either death or emigration. The DRG became completely regulated by the Nazi state, beginning with the removal of DRG president and political dissident Robert Kienbock (11). In the famed Charité Hospital in Berlin, home of the renowned pathologist Rudolf Virchow, many cancer researchers were expelled because of their Jewish heritage. In 1933, the Nazi sterilization law was enacted and was implemented surgically or with the use of X rays, emboldening the proponents of eugenics with proposals of sterilization for selected cases of hereditary disease. This brutality peaked in Auschwitz, where sterilization of entire ethnic groups was undertaken, and by the end of the war 350,000 people had been

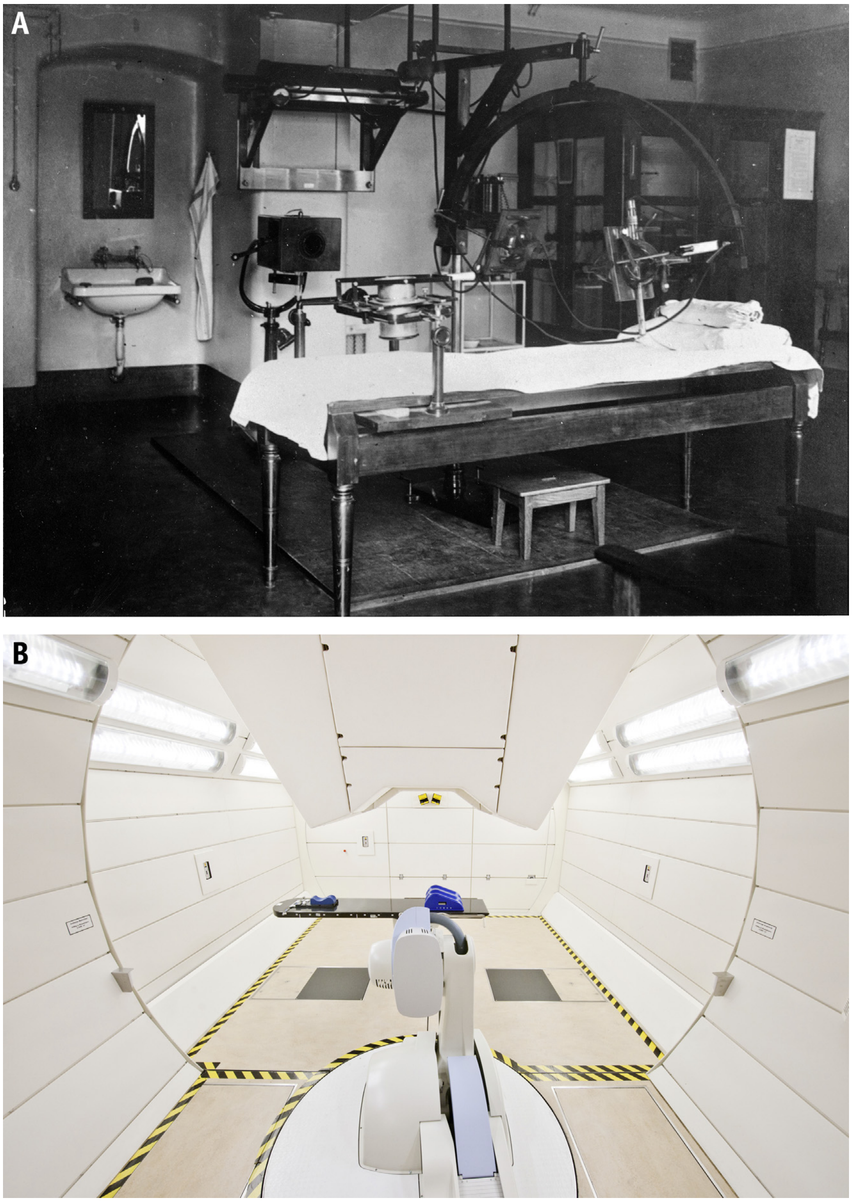

Fig. 4. (A) Radiation treatment room in the Institute for Experimental Cancer Research, ca 1912. (B) Modern radiation treatment room at the Heidelberg Ion Beam Therapy Center.

sterilized (12). The German medical community, which before the 1940s had boasted half of the world's Nobel Prizes and a large portion of the world's patents, was decimated by the Third Reich.

Equally disturbing and even more difficult to reconcile are the scientific initiatives fostered under Nazi fascism. The question became, as Stanford scientific historian Robert N. Proctor states, "What is this science that was allowed to flourish under fascism?" (12). In 1928, cancer surpassed tuberculosis as the second most common cause of death in Germany and was declared "the number one enemy of the state," thus becoming a focus of the rising Third Reich. Inherent within Nazi rhetoric were sordid, hyperracialized genetic theories, which existed as propaganda to further the regime's demographic prejudices. With the German scientific community in disarray, basic science research faltered. However, owing to the strict authoritarian Nazi hold on the country, aggressive public health initiatives were undertaken. In 1938, an intense propaganda machine for the early identification of colon, breast, and gynecologic cancer was waged, which was accompanied by the creation of a widespread German Cancer Registry focused on incidence and pathology (12). This Third Reich obsession with cancer population statistics must be interpreted with caution in light of the potential for abuse of such demographic data.

Antithetically, in this repressive Nazi era an open war was waged on the tobacco industry with an aggressive antitobacco campaign in the 1940s, which included public health outreach and education, advertising bans, and restrictions on public smoking. Much of this antitobacco fervor began with Fritz Lickint, who released epidemiologic data connecting smoking with lung cancer in 1929, published *Tabak und Organismus* in 1939, and became known as the physician "most hated by the tobacco industry" (12). Furthermore, other health initiatives were enacted to limit occupational hazards to asbestos, chromate, and aromatic amines, although foreigners and those of "undesirable demographics" were exempt from these safeguards. The chief physician of the German Labor Front, Hermann Hebestreit, also demonstrated a link between lung cancer and radium exposure in Joachimstal uranium miners in 1939 (12). During this period, rigorous radiation exposure regulations were enacted. Interestingly, these radiation safety initiatives were propelled forward by eugenicists, who fought with socialists who scoffed at the dangers of excessive radiation. Although progressive cancer preventative and management strategies were implemented for the "desirable" population, these same methods were ignored or used against those who were deemed enemies of the Nazi regime.

Cold War Divisions

Unconditional surrender on May 8, 1945, ended the efforts of the Third Reich, although the subsequent Allied occupation and fragmentation of Germany into East (German Democratic Republic) and West (Federal Republic of Germany) brought about new challenges. During this period, American, Scandinavian, and British scientific advances vastly outpaced those in Germany. Some of these foreign advances in radiation therapy were adopted in West Germany, yet in the German Democratic Republic USSR-enforced restrictions suffocated radiation therapy progress. Owing to economic restrictions imposed by the Soviet Council for Mutual Economic Assistance, the production of top-tier cobalt units in Dresden was abandoned in favor of construction of radiation therapy equipment in Czechoslovakia (11). These machines were of such poor quality that East German physicians were forced to import a handful of foreign units at high cost. In West Germany, scientific progress carried on, including the development of inverse treatment planning system optimization algorithms by German physicists Wilfgang Schlegel and Thomas Bortfeld of the DKFZ, to be used a decade later for intensity modulated radiation therapy (13).

Huge scientific leaps were also made in the field of particle physics. In 1953 the *Conseil Européen pour la Recherche Nucléaire* (CERN) convention was established and included West Germany as one of the founding member states (14). The *Gesellschaft für Schwerionenforschung* (GSI) was created in Darmstadt, West Germany, in 1969 and would become a center that established Germany as a leader in the clinical application of heavy ion therapy. Gerhard Kraft can be credited as the forefather of the modern ion therapy movement in Germany. Kraft was trained as a nuclear physicist and radiobiologist, and after graduating from the University of Cologne, he completed a fellowship at the Lawrence Berkeley Laboratory under the supervision of Cornelius Tobias. In 1981 he returned to Germany as a staff member at the GSI and introduced particle therapy to Europe. Kraft became the founder and director of the Biophysics Department at the GSI and eventually proposed a pilot project for the clinical use of ion therapy. This plan was implemented as a joint initiative of Heidelberg University Hospital, DKFZ, and GSI. Translation of basic science to clinical treatment at the GSI occurred in 1997, when the first patient was treated with carbon ions for a chordoma. From 1997 to 2008, more than 400 patients were treated with ion therapy at the GSI (14).

In November 1989, the fall of the Berlin Wall heralded the most productive scientific era in Germany since World War I, although the turbulent reunification led to marginalization of some East German physicians. In fact, many lost their positions in favor of often younger or less qualified West German doctors (11). In addition, a well-established East German cancer registry was disbanded by the West. Nevertheless, significant investments were made to improve the obsolete equipment in East Germany, and many subsidies continue into the modern era. In November 1995, the German Society of Radiation Oncology (DEGRO) was founded, led by its first president, Michael Bamberg, and so began the modern era of radiation oncology in Germany (11).

Modern Radiation Oncology in Germany

Health care system and structure

Bismarck's vision in the late 1800s has evolved into a shared German understanding of the fundamental pillars of health care: affordability, accessibility, and quality. The principle of solidarity, or *Solidaritätsprinzip*, of the health care system has survived world wars, political revolutions, and numerous health care and social reforms. Eighty-nine percent of the population pays into the community-based sickness funds, or *Gesetzliche Krankenversicherung* (GKV). Up to a certain income level, membership to the GKVs is obligatory, whereas residents with higher incomes and the self-employed may contribute as voluntary members. The remaining population uses private health insurance, thus ensuring complete coverage of the German population (15). Financing of the sickness funds is accomplished by shared employee and employer contributions totaling 14.6% of wages (16). Interestingly, services paid for by the GKVs must be defined as "necessary," with a scientifically proven benefit, and the costs must be deemed "reasonable" in relation to that potential benefit. This ability to tie reimbursement with assurance of standard-of-care delivery at an appropriate price is a paramount achievement, and continues to be sought after in the United States.

Medical education and radiation oncology training

Medical education in Germany dates back to 1386 with the establishment of Heidelberg University. Along with law, philosophy, and theology, medicine was one of the founding schools at Heidelberg. Germany's universities are in large part public institutions, with affordable tuition rates of approximately €60 per semester, ensuring accessible secondary education for the general public. Many independent entities, such as the Helmholtz Alliance and the Max-Planck Institute, also exist as autonomous nonprofit research organizations with loose cooperative affiliations with academic universities throughout Germany.

Medical education is highly competitive, with a limited number of positions; thus, many prospective students wait several years before acceptance. Studies are generally held in German, although English is used regularly as a consequence of standards in the international literature. In fact, English language education often begins in preschools, with mandated proficiency of at least one foreign language for university acceptance. Medical school consists of two preclinical years (*Vorklinik*), three clinical years (*Klinik*), and one practical year (*Praktisches Jahr*), each requiring satisfactory completion of a written or oral exam before advancement, culminating in a license to practice medicine in Germany (*Approbation*). To receive the academic degree Dr. med. (Doctor of Medicine), which is not mandatory, a candidate must additionally complete a scientific study and dissertation, either during medical school or after graduation.

After completion of medical school, physicians wishing to specialize in radiation oncology complete five additional years of training in academic hospitals to meet the eligibility requirements for specialist education. The application process for residency is free of charge and is not strictly regulated on a national level as is the match process in the United States. Encapsulated within radiation oncology training is a 12-month rotation through hospital wards. The ward experience is often specific to inpatient oncologic care and is taught in conjunction with medical oncology. As such, residents gain experience with the delivery and management of chemotherapy and are certified to deliver care independently at the completion of training. An additional 12 months may be completed in diagnostic radiology, although this is no longer required. In contrast to the United States, graduation from training does not come with a massive increase in salary, although this difference is offset in part by the virtually negligible student loans accumulated during training in Germany. Overall, 90% of German radiation oncology trainees have stated that they were very pleased with their decision to enter the field (17).

Particle therapy development

In an effort to expand the clinical application of particle therapy initiated at the GSI, the Heidelberg Ion Beam Therapy Center (HIT) opened in 2009 as a joint endeavor of the GSI and Siemens Medical Company (14). The HIT allows for clinical treatment with both proton and carbon ions, with future capabilities for helium and oxygen treatment. The HIT contains the world's first heavy ion gantry, housed in three stories and weighing over 600 tons (Fig. 5). It is one of only a handful of centers worldwide (Germany, Japan, Italy, and China) with the ability to treat patients with carbon therapy. Treatment with heavy ions has traditionally been reserved for radioresistant and locally aggressive tumors such as chordomas, chondrosarcomas, and adenoid cystic carcinomas or complex reirradiation cases. Under the direction of Jürgen Debus, more than 3600 patients have been treated at the HIT since 2009. New innovations including the active raster scanning technique, where particles are magnetically guided over the target volume and modulated in intensity, were developed at the GSI and implemented at the HIT (18). Additionally, the development of a quantitative calculation of relative biologic effects (RBE) using the theoretic local effect model (LEM) was established at the GSI, which allows for optimization of treatment planning according to biologic parameters and is regularly implemented for HIT treatment plans (19). Five additional proton centers are in clinical operation within Germany and include the Rinecker Proton Therapy Centre (Munich, 2009), the West German Proton Therapy Center (University Hospital Essen, 2013), the Ion Beam Laboratory at the Hahn-Meitner-Institute (Charité University Hospital Berlin, 1998), the Proton Therapy Center (University Hospital Dresden, 2014), and the Marburg Ion Beam Therapy Center (Marburg, 2015).

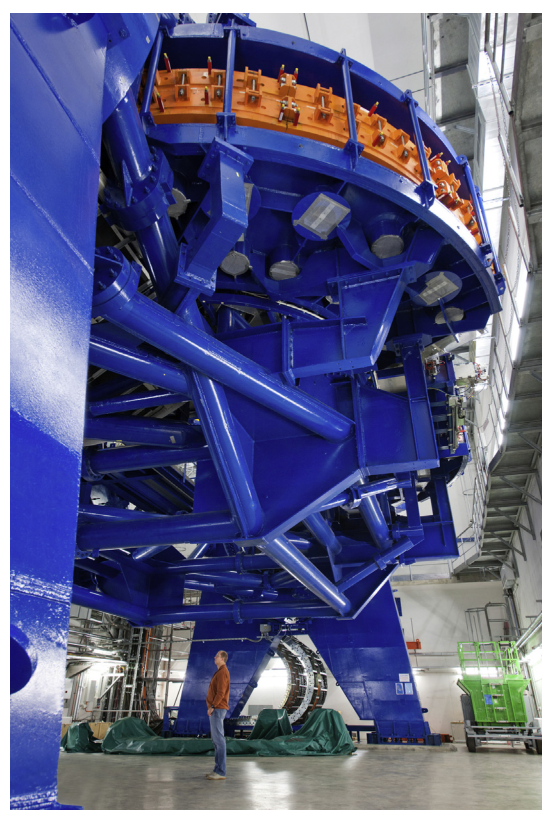

Fig. 5. Heavy ion gantry at the Heidelberg Ion Beam Therapy Center.

Future of radiation oncology in Germany

As particle therapy advances and accessibility expands, many of the same challenges found in the United States have manifested themselves in Germany. Although most radiation oncologists would agree that the physical dose distribution and perhaps the radiobiologic effect of protons is superior to that of photons, clinical data have yet to establish proton superiority. The substantial investments, particularly for carbon ion therapy, and the higher costs per treatment are currently not sufficiently justified by clinical data, particularly in view of the lack of direct comparisons with photon therapy in the phase 3 setting. However, in Germany the potential benefit of treatment with particle therapy for certain tumor types, including chordomas, chondrosarcomas, arteriovenous malformations, uveal tumors, adenoid cystic carcinomas, and pediatric malignancies, has been accepted by the GKV thus making full reimbursement ubiquitous.

Clinical implementation of carbon ion therapy is a rapidly expanding area of investigation with approximately 20 accruing phase 1 and 2 trials and two randomized phase 3 trials at the HIT. In addition, research into the application of helium and oxygen is currently focused at preclinical physics and radiobiological levels. Finally, investigation into advanced modalities of image guided radiation therapy prompted the German Research Foundation in 2016 to subsidize the commissioning of two magnetic resonance imaging—guided radiation therapy units at Tübingen University Hospital and Heidelberg University Hospital.

Conclusion

From the moment the first aberrant photons were revealed in Würzburg, the evolution of radiation oncology in Germany has taken the form of a medical *Bildungsroman*, undulating with the sociopolitical changes and challenges of the time. Germany now enters a new phase of scientific and medical exploration, although this era is not without its own challenges. Rising German health care expenditures, the fragility of the European Union, and a massive influx of immigrants promise to alter the dynamic of the German medical landscape for years to come.

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