Arabinda Kumar Rath
Narayan Sahoo *Editors*

Particle Radiotherapy

Emerging Technology for Treatment of Cancer

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Foreword

When Dr. A. K. Rath asked me to write the foreword for this book, *Particle Radiotherapy: Emerging Technology for Treatment of Cancer*, I was surprised because it has been nearly 20 years since I took voluntary retirement from Los Alamos National Laboratory to devote my time fully to provide appropriate radiation treatment for cancer with a hope that it could serve as a model for rural India. Earlier, for more than three decades, I devoted my work in the emerging field of particle radiotherapy during 1961–1995. Dr. Rath assured me that the observations made by me in my review papers nearly 20 years ago are still valid today and they need to be in the foreword of this book. My first interaction with Dr. Rath was nearly 10 years ago when he invited me to make a presentation during AMPICON 2006 held in Bhubaneswar where I spoke on 'Our Spiritual and Professional Heritage: Opportunity and Challenge for Medical Physicists of India in the New Millennium'. I had expressed my hope that the emerging technologies would meet the challenges in this New Millennium.

I understand that this book is intended primarily for those engaged in the application of radiation in the treatment of cancer. The leading article 'Particle Radiotherapy: An Introduction' by the editor Dr. A. K. Rath provides a good introduction on the increasing global interest in this millennium. Various international experts in the field of proton and carbon-ion radiotherapy have provided interesting chapters on the latest developments as well as challenges ahead in implementing the best form of proton and carbon-ion therapy in a robust manner.

I find it interesting to note that both the editors of this interesting book hail from the state of Odisha, one of the historic states of India: Dr. A. K. Rath is a senior medical physicist in India and Dr. Narayan Sahoo is a senior medical physicist working with protons at M.D. Anderson Cancer Center in the United States. Both are familiar with the challenging problems in providing appropriate cancer care for all the needy patients as pointed by a series of interesting articles on global health in the July 1, 2014 issue of the *Red Journal*.

I would briefly present the early historical beginnings of particle radiotherapy and the challenges we need to face in providing appropriate radiation treatment to all the cancer patients, especially those in rural India.

Particle therapy has a very long history, starting with fast neutrons during the mid-1930s. The idea of using protons also predates the introduction of Cobalt-60 which provided immense relief to a very large number of cancer patients globally at affordable cost, relative simplicity and robustness in

treating patients. Unfortunately, cobalt machines are getting replaced prematurely, especially in developing countries including India, due to reasons other than in the best interests of patients that need appropriate treatment at affordable costs.

Dr. Robert Wilson in the year 1946 published the first paper formally proposing protons in an elegant manner. It was a classic paper that needs to be studied by everybody working in this field. I had the pleasure of knowing Dr. Wilson and learned from him directly the timing and circumstances in which his idea of using protons for cancer treatment arose. It is worth noting that he was part of the Manhattan Project in Los Alamos, which was assigned with the task of building nuclear weapons. Dejected by the aftermath of Hiroshima and Nagasaki bombings, he became interested in doing science for the benefit of mankind. He joined the cradle of 'big science', the Radiation Laboratory of Ernest O. Lawrence at Berkeley. Thus one can see the beginnings of proton radiotherapy were also idealistically similar to the beginnings of radiation treatment of cancer by Roentgen, Madam Curie, L.H. Gray and several others.

During the early 1970s, with the declaration of war on cancer by the then United States President Nixon, considerable funding was available and it gave a big boost for clinical use of neutrons, negative pions (pions), and heavy ions. I had the privilege of conducting pre-therapeutic experiments on dosimetry and radiobiology of pions and heavy ions during the 1960s in Berkeley. Thereafter I continued comparative studies over the next two decades at Los Alamos National Laboratory using clinically relevant protons, heavy ions, pions and fast neutrons with the support of the U.S. National Cancer Institute.

The decade of the 1970s witnessed heavy competition for funds from different institutions. The interest in fast neutrons was revived by the clinical reinvestigations of fast neutrons and the eloquent arguments of Dr. Jack Fowler on the efficacy of fast neutrons in dealing with hypoxic cells in the tumor. The radiotherapy community at that time was inclined more towards the importance of reduced oxygen enhancement ratio (OER) achievable with fast neutrons and with the expectation of even more reduced OER with heavy ions and pions.

Although dose localization is an important factor in radiotherapy, proton beams did not get adequate attention during the 1970s in spite of their superior dose localization. Interestingly, Dr. Robert Wilson, the first proponent of protons for radiotherapy, was heading the National Accelerator facility near Chicago at that time and was approached by the radiotherapy community around Chicago to provide them with a neutron beam which is relatively complex to produce compared to protons. Accordingly, neutron beam was provided to them. The number of fast neutron facilities in the world increased rapidly to nearly 20 during 1970s reaching a plateau during the 1980s, while the number of proton therapy facilities remained to be only about five along with a few pion and heavy ion physics facilities that were very complex and expensive. Also, there was considerable interest among accelerator engineers in designing pion and heavy ion facilities dedicated to medical purposes although the clinical evidence was lacking. Some of us in the field even at that

time advocated the importance of clinical studies of protons by building medically dedicated facilities while research continued with pions and heavy ions using physics facilities.

I had the privilege of doing comparative studies of particles using therapeutically relevant beams for the first time and they revealed that the oxygen enhancement ration (OER) of heavy ions and pions were much higher than the expected low OERs on the basis of studies from low energy heavy ions. The U.S. National Cancer Institute with a select group of scientists called in a special meeting at Massachusetts General Hospital, Boston, around 1977 to discuss my new results since they were considering several proposals for funding to build medically dedicated accelerators at that time. Naturally, my findings were not palatable for some people planning to build medically dedicated pion and heavy ion facilities. Fortunately for me several other investigators repeated these measurements and obtained similar results. I had the privilege of participating in various international cooperative meetings in the field of particle therapy. In some of these meetings, whenever appropriate, based on my research findings, I stressed the importance of using protons clinically by building medically dedicated proton therapy facilities during the 1970s, at a time protons were not so popular compared to esoteric pions and heavy ions.

After 80 years of research, fast neutrons finally proved to be the treatment of choice for advanced salivary gland tumors through randomized trials in several countries. Two cyclotrons for neutron therapy were specially built with the funding from the US National Cancer Institute: one in M.D. Anderson Cancer Center, Houston, and another in the University of California, Los Angeles, so that these two special facilities can serve most of the patients with advanced salivary gland tumor since it is relatively a rare tumor. Ironically, both these cyclotrons were shut down due to lack of referrals from other medical centers, indicating that there are several other human factors besides scientific knowledge in taking proper care of cancer patients. Neutron therapy discontinued globally.

Another interesting experience came from the use of pions for radiotherapy. In spite of its interesting and unique star formation near the end of their tracks, pions were not found to be superior to the conventional radiotherapy by the group in Vancouver, Canada. The pion therapy programs in Los Alamos, USA, and Villigen, Switzerland, also discontinued. Even the famous scientists including Fermi thought that pions are ideal for cancer treatment. This clearly indicates that the potential advantage on the basis of physics and radiobiology alone is not sufficient proof for clinical improvement, which is much more complex. In some ways, this negative result is a blessing since we do not need such expensive machinery for cancer care. Among heavy ions, only carbon ions are being used rather than heavier ions such as neon that was used earlier in Berkeley during the 1980s probably because of the propensity of late effects to normal tissues.

Thus, in the particle therapy race among the particles, neutrons, protons pions and heavy ions, protons, in spite of the very low start in early 1970s, is the only main survivor. However, caution is required because of the unusual multiplication of proton therapy machines globally including in developing

countries in this New Millennium. Dr. Mazal and his associates in their chapter 'Physical Rationale for Proton Therapy and Elements to Build a Clinical Center', in this book, made an interesting comment: there are about ten companies that are bidding to build proton machines for cancer centers, much more in number than for Linacs with a caution for long term prospects for servicing due to potential danger for the survival of some of these competing companies.

The future course of proton radiotherapy needs thoughtful and collective guidance by the organizations such as PTCOG, which was technically very effective. Randomized trials comparing proton therapy are in progress with the best form of conventional radiotherapy, which is becoming increasingly formidable.

It is natural for developing countries to try to be in the forefront in emerging fields. Radiation therapy continues to be one of the main forms of cancer treatment and hence it is important to provide this much needed treatment to all the needy patients in a cost effective manner while continuing to participate and contribute to the modern developments to improve the human condition. It is ironic that I stress now on the importance of providing appropriate radiotherapy for all the needy patients after having spent most of my research career in the field of using particle therapy.

I hope that India with its increasing burden of cancer patients, growing strength of entrepreneurs and rich cultural heritage of caring for the sick and old will come up with solutions for cancer treatment worthy of emulation by developing nations of the world.

I would like to conclude with the following quotation:

> "The men who are cursed with the gift of the literal mind are the unfortunate ones who are always busy with their nets and neglect the fishing". Rabindranath Tagore

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Preface

The success of clinical radiotherapy is judged by the extent of complication free tumor control it can provide. In the current practice of radiotherapy, very precise methods of image-guided intensity-modulated beam delivery can be used to deliver highly conformal radiotherapy to the target. However, normal tissue tolerance remains the main limiting factor in delivering sufficient dose to the target to maximize the tumor control probability (TCP). Developments in radiotherapy are driven by the desire to find suitable modalities and techniques to reduce dose to the normal tissue leading to lower normal tissue complication probability (NTCP) that would allow delivery of higher dose to the target to improve the therapeutic gain. Therapeutic beams of particles like C-12 ion and proton (referred as particles in this preface and in other chapters of this book) are attractive options to achieve this goal because of their ability to reduce the dose to the critical organs and normal tissue due to their finite range in the tissue-like media. The availability of discrete scanning C-12 and proton beam delivery technology has also made intensity-modulated particle beam therapy possible. There is a growing interest in clinical practice to utilize these modalities to improve the efficacy of the radiation therapy. Although the dose distribution of particle beam in water medium is precisely known, many aspects of physical and biological effective dose distribution inside the patient remain uncertain. The particle beam dose distribution is more sensitive to small intra-fraction and inter-fraction changes in the patient anatomy, setup errors, and internal organ motion. There are ongoing efforts to design treatment plans to mitigate some of the physical and biological uncertainties in the treatment planning process. Further improvements in the efficacy of the particle beam therapy will depend on our ability to reduce these uncertainties through the knowledge gained from past clinical experience and future research endeavors. Keeping this in mind, a daylong symposium was organized in November 2013 in Kolkata, India, to hear the views of leading experts on the current state of the art and future developments of the delivery system, dosimetry, treatment planning, and radiation biology for particle therapy. The idea to publish a book based on the material presented at the symposium and with some additional chapters was conceived to share the

knowledge and wisdom of these experts with the wider community interested in radiation oncology. This book starts with a foreword by Dr. M. Raju who made many groundbreaking contributions to the early development of particle therapy. Dr. Rath, one of us, provides as essay in Chap. 1 on the historical developments and his views on the future directions of particle therapy using his vast knowledge gained both from attending many national and international conferences on this subject and from close interaction with many experts in the field. Dr. Mohan, who has made many seminal contributions to the field of radiation oncology physics and proton therapy, and his co-authors share their expert views on the future developments to improve the efficacy particle therapy in Chap. 2. IBA is the world's leading vendor of the proton therapy delivery system. The current state of the art and future developments in the beam production system are described by Dr. Emma Pearson et al. from IBA Medical Accelerator Solutions: R&D Department in Chap. 3. Japan is a leader in the use of the C-ion therapy. In Chap. 4, Dr. Koji Noda, the Director of the Accelerator and Medical Physics Department of the National Institute of Radiological Sciences in Chiba, Japan, describes his experience in the development of C-ion therapy technologies in Japan. Dr. Mazal is the Head of Medical Physics of Institut Curie, Paris, France, including the Proton Therapy Center in Orsay (CPO). He and his colleagues from France share their expert knowledge on the physics, biology, technology and clinical indications for proton therapy, and logistics to build a clinical proton therapy facility in Chap. 5. In Chap. 6, Dr. Sahoo, one of us, and his co-authors provide a review of the radiation dosimetry in proton therapy. Dr. Marco Schwarz, a leading expert on the clinical proton therapy, and his colleagues from Trento, Italy, describe their perspective of the current and future clinical use of the proton pencil beam scanning technology in Chap. 7. Dr. Kooy is a well-known expert on the clinical use of proton therapy and is involved in the development of new generation of proton therapy treatment planning system. Chap. 8 provides his insights about the treatment planning for protons. Dr. Jäkel is the Medical Physics Director of the Heavy Ion Therapy facility in Heidelberg, Germany, and is a well-known expert on the heavy ion therapy physics. His perspectives of radiation therapy with protons and heavy ions are given in Chap. 9. Robust optimization of treatment plans is considered to be essential to mitigate range, set up, and internal organ motion related uncertainties in particle therapy. Dr. Liu, an expert on robust optimization, describes the current practice and future developments in robust optimization and robustness quantification methodology for proton therapy planning in Chap. 10. One of the attractive features of particle therapy is their higher radiobiological effectiveness (RBE) on cell kill compared to photons used in external beam radiotherapy due to higher linear energy transfer during the energy deposition process. However, the uncertainties in the RBE values of particle beams are large and more work is needed to find their clinically relevant values. Dr. Matsufuji is a leading expert on modeling and analyzing

the biological and clinical effectiveness of the carbon ion therapy. He shares his insights on the modeling of biological effective dose for carbon ion therapy in Chap. 11. Most of the new proton therapy facilities are equipped with pencil beam scanning because of its ability to deliver more conformal dose to the target compared to the passively scattered proton beam. In Chap. 12, Dr. Lomax, a well-known expert on proton pencil beam scanning technology, describes the methodology for planning and mitigating the range and motion related uncertainties in this popular proton therapy modality. In summary, this book covers important aspects of physics and radiobiology, delivery system, facility design, treatment planning, and future directions for particle therapy. It is our sincere hope that readers will find this book as a useful resource for their professional endeavors related to particle therapy.

We express our sincere appreciation of the efforts of all the authors in writing their chapters. We are also thankful to many people at Springer who were involved in the publication of this book. We are happy that this book is published, and is in the hands of interested readers who are aspiring to gain some knowledge or information from the collective insights of the authors of different chapters.

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Contents

Particle Radiotherapy: An Introduction

1

Arabinda Kumar Rath

There were 14.1 million new cancer cases, 8.2 million cancer deaths, and 32.6 million people living with cancer (within 5 year of diagnosis) in 2012 worldwide [1]. From 1954 through December 2014, a total of 137,179 patients across the world have been treated with all forms of particle therapy since it was first started in Berkeley in 1954 [2]. Presently particle radiotherapy treatment constitutes about 1 % of the total number of patients receiving radiotherapy worldwide. In the recent past, there is a significant interest by all stakeholders in this decades old technology and the chance that it will emerge as a technology of choice as a prime modality of cancer treatment is very high. The book is an attempt to have a closer look on what are the physical and biological factors that make particles the choice of radiotherapy and the clinical evidence that are slowly pouring in from the exponentially growing number of particle therapy centers worldwide treating cancer patients.

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1.1 History of Development

Treatment of cancer using ionizing radiation was started soon after the discovery of X-rays by Roentgen in 1895. The first such successful treatment of cancer with cure has been reported to have been achieved as early as July 4, 1899, in Stockholm [3]. Photons or X-ray therapy that dominated radiotherapy for the first half of the last century can be broadly classified into three phases as superficial therapy (10–150 KV), deep (or orthovoltage) therapy (200–300 KV), and megavoltage (or super voltage) therapy (above 1 MV). High-energy X-rays (photons) especially with the Linear Accelerator technology has led to the success of radiotherapy as one of the primary modality of cancer treatment in the last three decades. Ernest Rutherford first coined the term "proton" and reported its existence 1919. The first reported literature of particle acceleration dates back to 1936 when Lawrence developed the first cyclotron in Berkeley, and later he built a 37 in. cyclotron by the year 1939 for which he was awarded the Noble Prize the same year. Robert Wilson wrote a classic paper in 1946 that suggested the potential use of particle beams for treatment of cancer. Using the 184 in. cyclotron developed in Berkeley, the first proton therapy treatment was delivered in 1954 and was used for patient treatment till its decommissioning in 1987. Similar efforts were made in Uppsala Sweden, and patient treatment with 185 MeV

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proton beam was undertaken from 1957 to 1968. The Harvard Cyclotron was used for patient treatment from 1959. Particle therapy started in Russia in 1967, in Japan in 1979, and in South Africa in 1993. The first hospital based proton therapy facility was built in Loma Linda University in the USA in 1990 and has been treating patients since then.

1.2 Physical Basis of Particle Therapy

Therapeutic use of protons was first suggested by Robert R Wilson in 1946 [4]. The depth dose curves of protons are completely different from those of photons (X-rays) because these charged particles have very little scattering when penetrating the matter and give the highest dose near the end of their range which is known as the "Bragg peak" after which there is drastic fall of dose within a short distance (Fig. 1.1). Much before the clinical success of today's megavoltage X-rays (photons) in precision radiotherapy, it was pointed out as early as in 1974 that on the basis of the physical factors such as higher LET (Fig. 1.2), the particles of choice for radiotherapy are protons or helium ions [5]. At Harvard a comparison of the dose distribution of protons to Co-60 gamma rays and 22-MeV photons from a betatron was done [6]. They found out that the dose to normal tissues outside the treatment volume is about 70 % of the tumor dose when Co-60

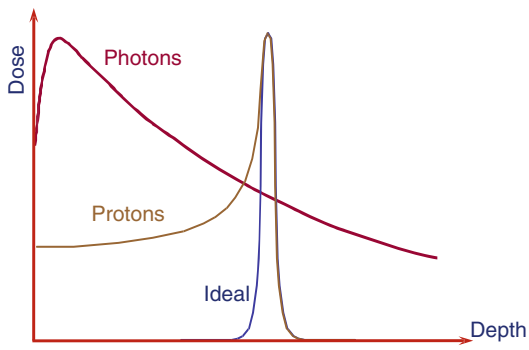

Fig. 1.1 Depth dose characteristics of Photons Versus Protons showing the "bargg peak" in protons which is much closer to the ideal beam in external beam radiotherapy.

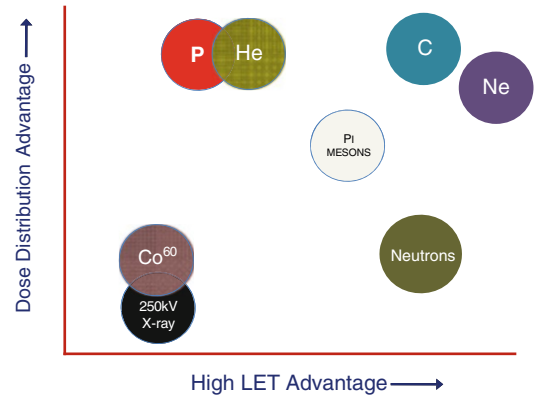

Fig. 1.2 Dr Raju's idea demonstrating the relative advantage of particles proposed in 1974 representing the relative merits of high Linear Energy Transfer (High LET) particles

gamma rays are used. This normal tissue dose is reduced to about 40 % when 22-MeV X-rays are used, and this is reduced further to about 22 % when protons are used. In addition, the dose with protons can be made more uniform throughout the treatment volume including the edges. Thus, using multiport proton irradiation, the dose given to all of normal tissues can be reduced even more than that achieved with 22-MeV X-rays. They had shown that the use of high-energy protons or other heavy-charged particles makes possible substantially improved control of the geometric distribution of therapeutic radiations over that obtainable with super-voltage X-rays or electrons and suggests the possibility of better clinical control of some types of malignant lesions with reduced complication rates. Sufficient clinical experience with protons has already been obtained to show that their effects are not markedly different from those of high-voltage X-rays if equal radiation doses are compared. In a review [7] of the physical, technical, radiological, and clinical status of proton therapy, it was reported that protons produce effects similar to those of X-rays, but dose distribution and range make protons more flexible and useful therapeutically. The ability to confine the major fraction of proton absorbed dose to a designated volume allows the decrease of dose to normal tissue or the increase of dose to the cancer. Improved dose distribution is quantified by determining the ratio of normal

tissue dose for X-rays to that for protons in different treatment plans. Normal tissue integral dose from X-rays therapy is generally 2–5 times as high as that anticipated from proton therapy.

1.3 Facilities and Patients Statistics

Exact up-to-date statistics are available from PTCOG for each of the treating facilities all over the world. The numbers for each type of particle treated so far in the world are as follows. Patients treated with He are 2054 (1957–1992), with pions are 1100 (1974–1994), with C-ions are 15,736 (1994 to present), with other ions are 433 (1975–1992), and with protons are 118,195 (1954 to present) which makes the grand total as 137,179 as of the end of 2014. Of the total of about 137,000 patients treated with particle therapy worldwide from 1954 to 2014, 15,400 were treated in 2014 alone making it more than 10 % being treated only in last 1 year. In 2014, about 10 % of patients were pediatric and another 10 % were treated for ocular melanomas. Forty-eight particle therapy facilities were in clinical operation at the end of 2014. Of the total cases treated worldwide with particles, 86 % are treated with protons and 14 % are treated with carbon ions and with other particles. Five new particle therapy centers started patient treatments in 2014. This again is more than 10 % increase in facilities in 1 year. Further as on date, more than 30 more new particle therapy centers are under construction that will add about 80 treatment rooms in the near future. They are spread out all over the world with half of these are in the USA and one-third are in Asia. In 2015 about 15 centers were expected to start commissioning, and about half of them were planning to start treating patients before the end of 2015.

These figures are impressive and growth story of particle radiotherapy is truly exponential. Now there is a school of thought that as the ancillary technology for particle therapy is maturing now these data will further get strengthened and as the integrations become better we will have more success stories following in the near future. But there is another school of thought that we are having only incremental benefits which are very small and do not justify the kind of cost that a particle therapy facility requires. Though the growth story is impressive, will particle therapy be a viable alternative to photons if not replace it completely is a question that is still to be answered. The physics of particle radiotherapy has been a promising one since the beginning, but in an era of cost consciousness, the debate is should the limited resources of healthcare be spent on a technology which is expensive and may be the most expensive in medical sciences ever. Several of the authors in this book have pointed out as part of their discussions by quoting several studies of theirs as well as others that there are promises and pitfalls in particle radiotherapy. The real challenge today is to make this theoretically superior technology accessible and affordable to millions of cancer patients worldwide.

1.4 Physical Advantages Versus Clinical Realities

High LET radiation from particles as a more effective alternative to photons for routine clinical treatment of resistant tumors has not yet been addressed to the satisfaction of the medical fraternity. The reason for this is that though the physics of particles and their dose deposition capabilities are well understood, delivering them safely to the desired target area in a patient, the dose response and complications thereof are not fully understood. A considerable progress though has been made in understanding the radiobiology of the different particles that includes proton, carbon ions, helium ions, pi mesons, and neutrons initially proposed as choice of particles for radiotherapy [8]. High-energy X-rays (photons) have reached a point of saturation in radiotherapy; it is evident that they cannot further be improved only on the basis of dose distribution advantages. It is only with protons and particles (light and heavy ions) that we will be able to get further dose distribution advantages. Increasing radiation dose to tumor increases tumor control probability leading to higher cure rates in cancer. This was well

recognized almost half a century ago that there is no "tumoricidal threshold dose," and the higher the dose, the higher is the probability of radiation-induced cell killing [9]. Recent data from dose escalation studies with protons [10] in a randomized controlled trial shows superior long-term cancer control for men with localized prostate cancer receiving high-dose versus conventional-dose radiation. This was achieved without an increase in grade ≥3 late urinary or rectal morbidity. Similarly treatments with carbon ion have already shown significant improvements in local control as well as improved survival rates as has been reported by the working Group for Lung Cancer in Japan with carbon ion radiotherapy for stage I non-small cell lung cancer study [11] more than a decade ago.

Is the field of particle therapy a "trap" for physicists and engineers who want to solve everything in a hurry as was put in a candid way by Dr MR Raju [12] almost two decades ago after working in the field for three decades. Let us ask the fundamental question "has radiotherapy helped cancer control?" The answer is a big and emphatic "yes." It was recognized in early parts of the last century that radiation possesses very high tumoricidal effect. That has propelled a century of research in radiation therapy to localize and deliver the radiation precisely to the tumor or cancer cells called as targets. All forms of radiotherapy have always focused on this fundamental concept. As the energy of photons increased from the kilo voltage level to megavoltage level, it was realized that higher photon energy per se will not be making therapy more effective. After reaching optimum energy level, research was focused on target definition and ability to contain the radiation to the boundaries of these targets. Simultaneous developments in imaging and computational power helped bridge the gap better, and the era of conformal radiotherapy was born. The last two decades since the mid-1990s, which is the era of IMRT and IGRT, have witnessed quantum leaps in radiotherapy with photons. Higher number of fractions which were used to reduce complication is no more the norm, and hypofractionation with unconventional fractions ranging from single to five or seven has now become the norm for delivering radiation with stereotactic body radiotherapy (SBRT). It is now realized that photons have limitations and can no more be tailored to achieve further dose escalation by the current methods of delivery.

Recent reports suggest that disregarding relative biological effectiveness (RBE) variations might lead to suboptimal proton plans giving lower effect in the tumor and higher effect in normal tissues than expected [13]. As per the current assumption of RBE = 1.1, higher doses to the tumor and lower doses to the normal tissues were obtained for the proton plans compared to the photon plans. In contrast, when accounting for RBE variations, the comparison showed lower doses to the tumor and hot spots in organs at risk in the proton plans. These hot spots resulted in higher estimated NTCPs in the proton plans compared to the photon plans. For cases where the target is situated close to structures sensitive to hot spot doses, this trend may lead to bias in favor of proton plans in treatment plan comparisons. This has called for re-discussion on the role of variable relative biological effectiveness (RBE) in particle therapy, and it is now becoming more and more evident that for various end points of clinical relevance the biological response is differentially modulated by particles as compared by photons [14]. Thus, the presumptions like RBE of 1.1 for protons for the whole radiation field can no longer be used to predict response. In fact it is proposed by several pioneers in the field that biological modeling rather than physical dose modeling is going to be the way of treatment planning in the near future of radiotherapy.

1.5 The Cost Factor

The success of the last two decades of photon therapy has however not been translated directly into the success of particle therapy primarily due to some of the important factors like technology of particle therapy which is too expensive at present. Even among particles, there is a

significant difference in cost between the proton therapy and carbon ion therapy. The particle accelerators are basically high-end physics research equipment and not a routine hospital equipment. Cyclotrons that were traditionally physics research installed in university and academic setups have now been downsized, but still the infrastructure costs are in several orders higher than the photon therapy facilities. The order of cost and complexity difference between the linear accelerator technology with photon delivery and those for protons are in a scale 10–20 times higher and those for carbon ions are in a scale of 100 times higher, making it difficult for becoming a routine hospital equipment. The proton therapy done primarily with cyclotrons is now custom made for therapy facilities helping cost reduction. But this has been done in the last decade and a lot more is yet to be done to reduce cost. The total number of all particle therapy centers has not yet reached 50 where as there are thousands of photon accelerators that are available in the field since the last two decades. The synchrotrons and synchrocyclotrons used for production of carbon ions are very expensive even today and are beyond the reach of hospitals. The complexity also demands higher number of qualified manpower, and it is just not possible to bridge this gap in a short period of time. The cost component being too expensive to build and too expensive to maintain still haunts the field of particle radiotherapy today.

1.6 Consolidation Phase and Future Outlook

But the good news is that proton therapy has gained attention as a primary modality of radiation therapy in countries like the USA. Academic centers like university hospitals as well as community hospitals have built or are in the process of building proton therapy centers primarily to achieve competitive advantages. Clinical outcome data that had come from the proton therapy center in the last decade were from older technologies like passive scattering proton therapy (PSPT). But the newer facilities are having better capabilities of delivery with modern technology of particle generation and are likely to be superseded by intensity-modulated proton therapy (IMPT). Initial data though smaller in number show improvement in dose distribution by IMPT [15] as compared to the best conventional photon radiotherapy that has been reported. Such physical data are likely to result in longer-term success clinically in proving particle therapy superior to photon therapy of the present day. With more and more centers coming up with IMPT facilities, there will be opportunity to justify the adoption of proton therapy in more number of clinical indications than those that are currently used in routine practice of particle therapy. Recently PTCOG have initiated multi institutional trials for different clinical sites that helps bringing parity in delivery techniques as well uniformity in clinical parameters that in turn will help better reporting of larger series of data which will help to accept the technology. The early adopters of protons in the USA were primarily focusing on prostate cancer treatment, but today the clinical investigations are spread over various sites and indications like oropharynx, macular degeneration, pediatrics, early lung cancer, primary liver cancer, early breast cancer, as well as locally advanced lung cancer.

The fact remains that clinical data as on date are too small and have not been able to justify the wide spread acceptance of protons and particle therapy worldwide. The refinements in technology and integration with better imaging, planning, and delivery techniques are taking place at a fast pace, and it is only in this decade there has been an exponential increase in clinical facilities as well as patient numbers with protons and particle therapy facilities worldwide. The century of research in radiation and decades of patient treatment with particles have helped the development of particle therapy as an important clinical modality for treatment of cancer for the present and future. Sparse clinical data due to few facility and prohibitively expensive technology however still continues to be a challenge for making particle therapy a common tool for cancer care. The last two decades' significant growth in facilities and