Strahlentherapie
und Onkologie

Aktuelles Forum

Value and Perspectives of Proton Radiation Therapy for Limited Stage Prostate Cancer

Reinhard W. Schulte, Jerry D. Slater, Carl J. Rossi Jr., James M. Slater[1]

Background: This review article will focus on clinical results and limitations of proton beam irradiation. Possible technological, biological and medical perspectives will be addressed.
Patients and Methods: A total of 911 patients with limited stage prostate cancer were treated with proton beam irradiation at Loma Linda University between 1991 and 1996. Endpoints of this evaluation were biochemically no evidence of disease survival (bNED) as well as acute and late treatment-related toxicity.
Results: The bNED survival rate was 82% at 5 years. Among 870 patients evaluable for late toxicity the following late effects were observed: Grade 3/4: 0%, Grade 2 rectal: 3.5% and bladder: 5.4%.
Conclusions: Despite relatively short follow-up times it seems justified to conclude that proton beam irradiation of prostate cancer can improve bNED rates by 10% and decrease Grade 2 late effects by more than 10%. There were no Grade 3 and 4 late effects.

Key Words: Proton beam irradiation · Prostate cancer · Toxicity

Möglichkeiten und Grenzen der Protonenbestrahlung bei lokal begrenztem Prostatakarzinom

Hintergrund: Es werden Möglichkeiten und Grenzen der Protonenbestrahlung kritisch beleuchtet. Zudem wird ein Ausblick auf mögliche technologische, biologische und medizinische Perspektiven im Zusammenhang mit der Protonentherapie aufgezeigt.
Patienten und Methoden: Grundlage der Auswertung bilden 911 Patienten mit einem lokal begrenzten Prostatakarzinom, die von 1991 bis 1996 an der Universität von Loma Linda eine externe Radiotherapie mit Protonen erhielten. Die Endpunkte der Untersuchung waren das biochemische rezidivfreie Überleben (bNED) sowie die akute und chronische Toxizität der Bestrahlung (RTOG).
Ergebnisse: Nach fünf Jahren betrug das bNED (Kaplan-Meier) 82%. Unter 870 für die Frage der Spättoxizität auswertbaren Patienten wurden folgende Nebeneffekte beobachtet: Grad 3/4: 0%, Grad 2 Rektum: 3,5% und Blase: 5,4%.
Schlußfolgerungen: Trotz der relativ kurzen Nachbeobachtungszeiten scheint der Schluß zulässig, daß die Protonenbestrahlung das biochemische rezidivfreie Überleben um ca. 10% zu verbessern und Grad-2-Späteffekte um mehr als 10% zu senken vermag. Grad-3/4-Toxizitäten wurden überhaupt nicht beobachtet.

Schlüsselwörter: Protonenbestrahlung · Prostatakarzinom · Toxizität

Proton therapy in conjunction with 3-dimensional (3D) treatment planning is a promising radiation treatment technique, which is based on the premise that improved precision in dose delivery and tumor definition will enhance outcomes by maximizing the dose delivered to the tumor area while minimizing dose to normal tissues. The physical advantage of proton therapy over X-ray and electron beam therapy is due to the fact that the maximum dose occurs at depth opposed to close to the surface (Figure 1). This allows normal tissue sparing to a far greater extent than traditional radiation modalities.

Almost 9 years have passed since the first cancer patient was treated at Loma Linda University Medical Center, the world's first facility dedicated to the application and further development of 3D conformal radiation therapy using protons. Since that time, over 4,000 patients have completed treatments and the facility currently treats more than 60 patients per day.

The application of protons was first suggested by the Harvard physicist Robert R. Wilson, who published a historical landmark paper in the journal Radiology in 1946 [25]. Sixteen years earlier, Ernest O. Lawrence, a physicist at Berkeley, had invented the cyclotron, a circular particle accelerator, which could speed up charged particles such as protons to high energies. The 1940s saw the birth of large cyclotrons such as the 184-inch cyclotron at the University of California Berkeley, which was completed in 1946, and the Harvard cyclotron, which was constructed in 1948. Shortly after Wilson

[1]Department of Radiation Medicine, Loma Linda University Medical Center (LLUMC), USA.
Manuscript revised by G.G. Grabenbauer, Erlangen, Germany.
Submitted: 1 Nov 1999.
Accepted: 24 Nov 1999.

had published his paper, the 184-inch cyclotron was made available to a group of researchers with interest in biomedical applications of protons and deuterons, including Tobias, a Berkeley physicist, and John H. Lawrence, the physician brother of Ernest Lawrence. Because of the inability to accurately define tumor and normal tissue boundaries using the imaging methods available at that time, both John and Ernest Lawrence discouraged the use of the cyclotron for cancer treatment. The first application of charged particle beams in humans in 1954 was for pituitary hormone suppression in the treatment of patients with metastatic breast carcinoma [24].

Throughout the 1950s and 1960s, initial clinical studies with protons were also conducted at other physics accelerator laboratories around the world: the Gustaf Werner Institute in Uppsala, Sweden, the Harvard cyclotron in Cambridge, Massachusetts, the Physics Research Institute in Dubna, Russia, and the Institute for Experimental and Theoretical Physics (ITEP) in Moscow, Russia. For the reasons stated above, most of these early patients had small pituitary tumors and arteriovenous malformations, which could be localized with the help of orthogonal X-ray films. Another window of opportunity for protons opened during the early 1970s, when proton beam irradiation was first used for treating uveal melanomas at the Harvard Cyclotron in Cambridge, Massachusetts. The technique was soon recognized to cause tumor regression while preserving the eye [8]. By 1987, over a thousand cases had been treated at the Harvard cyclotron alone, in addition to many other cases treated with protons at the Paul Scherrer Institute in Switzerland and in Russia.

Fractionated proton therapy of larger tumors in different sites of the body had to await the development of sophisticated 3D imaging methods such as CT and MRI to accurately delineate the tumor volumes that could not be localized by other means. Furthermore, only a few of the proton accelerators involved in therapy had sufficient energy to reach tumors at all sites within the body. During the 1960s, Larsson, Graffmann, and colleagues at the Gustaf Werner Institute in Uppsala, Sweden, were the first to develop innovative proton treatment techniques for large field radiation therapy [7], for which they used the 185 MeV proton beams generated by a synchrocyclotron. However, only a small series of patients were treated with larger proton fields at that time.

During the 1970s, Suit, Goitein, and their associates from the Massachusetts General Hospital in Boston in collaboration with Koehler, the director of the Harvard cyclotron, initiated a treatment program for fractionated proton therapy of large tumors that could be reached with the 160-MeV beam of the Harvard cyclotron. For this program Goitein and his colleagues, for the first time, developed and applied 3D treatment planning techniques based on CT [6]. The excellent results produced by this program, in particular, for aggressive tumors of the base of skull [1], contributed significantly to the steadily rising interest in proton therapy worldwide.

Up to the end of the 1980s, all proton treatments had been delivered in physics laboratories using beams from accelerators that were designed for particle physics research and not for patient treatments. In 1985, an international group of physicists, physicians and other scientists, Proton Therapy Co-Operative Group (PTCOG), was formed, and plans to build a medical proton facility at Loma Linda University matured [22]. These plans succeeded in October of 1990 when the first clinically configured proton synchrotron began treating patients at Loma Linda University Medical Center (LLUMC).

Clinical Experience

The success of proton therapy critically depends on its ability to deliver an optimum dose to a well-defined target volume with a minimal dose to a surrounding critical normal tissue. After 9 years of treating patients with proton therapy at Loma Linda, clinical experience has accumulated for many tumor sites and certain non-malignant diseases [4, 9, 10, 16, 21, 28, 29] (Table 1). This experience allows a critical review of the overall benefit of proton therapy. In this respect, 2 main outcomes have to be assessed: tumor control probability and normal tissue complication probability.

At Loma Linda, the largest clinical experience has been gained with the treatment of prostate cancer. In the US, over 300,000 new cases of prostate cancer, and over 40,000 prostate-cancer-related deaths were estimated for 1997. The incidence of prostate cancer has increased markedly in the past decade mainly because of more frequent use of prostate-specific antigen (PSA) testing and a rapidly growing population of men of 80 years and older. Prostate cancer will be used here to demonstrate and to critically review the clinical results of proton therapy.

Tumor Control

Since 1991 proton beams have been used for the treatment of prostate carcinoma at Loma Linda University Medical Center [21, 29]. Through December of 1996, 911 patients with clinically localized prostate cancer had been treated either with protons alone or with a proton boost to the prostate in addition to pelvic irradiation with photons. The characteristics of these patients are summarized in Table 2. Treatments were planned with a 3D planning system; patients received 74 to 75 CGE (Cobalt Gray Equivalent) at 1.8 to 2.0 CGE per fraction.

CNS	Brain metastases Gliomas Arteriovenous malformations Pituitary adenomas Meningiomas Acoustic neurinomas
Base of skull	Chordomas Chondrosarcomas
Eye	Uveal melanomas Age-related macula degeneration
Head and neck	Nasopharyngeal tumors (primary and recurrent) Oropharyngeal tumors (locally advanced) Paranasal sinus tumors
Lung	Non-small-cell lung cancer
Pelvis	Prostate cancer
Pediatic	Neuroblastomas Wilm's tumors Orbital rhabdomyosarcomas Retinoblastomas Malignant CNS tumors

Table 1. Spectrum of conditions treated with protons at LLUMC.

Tabelle 1. Behandlungsindikationen zur Protonenbestrahlung in Loma Linda.

	Patients (%)
Clinical stage (T)	
Tla/lb	29 (3.2)
T1c	211 (23.3)
T2a	215 (23.7)
T2b	206 (22.7)
T2c	205 (22.6)
T3	40 (4.4)
Gleason score	
2 – 4	130 (16.3)
5 – 6	424 (50.2)
7 – 10	244 (30.6)
Initial PSA, ng/ml	
< 4.0	76 (8.8)
4.1 – 10.0	432 (50.2)
10.1–20.0	244 (28.3)
> 20.0	109 (12.7)

Table 2. Prostate tumor characteristics.

Tabelle 2. Charakteristika der Prostatakarzinompatienten.

The most recent analysis of study results was performed in June of 1999. At that time, follow-up data were available in 909 patients with a median follow-up of 39 months (range, 4 to 87 months). The main outcome measure was the Kaplan-Meier estimate of the freedom from biochemical failure (bNED) at 5 years after proton treatment. Patients were said to be free from biochemical recurrence when they had at least 24 months of follow-up without evidence of rising PSA and clinically no signs of disease progression. Biochemical recurrence was defined as 3 consecutive rises of PSA (> 10%) or any rise great enough to provoke the initiation of androgen treatment.

The overall estimated rate of bNED at 5 years was 82.2% (95% confidence interval, CI, 79.1% to 85.2%). On multivariate analysis, tumor stage, Gleason score, and pretreatment PSA level correlated significantly with the 5-year bNED rate. The 5-year bNED rates were significantly higher in patients with smaller tumors, lower Gleason score, and lower pretreatment PSA.

Complications

Acute toxicity in the patients treated with proton therapy for prostate cancer has been minimal. All patients completed their planned course of therapy as outpatients. At the time of analysis, 870 patients with at least 1 year of follow-up were available for evaluation of late toxicity. None developed Grade 3 or 4 gastrointestinal or genitourinary toxicity. Using the RTOG scale, the actuarial incidence of Grade 2 gastrointestinal symptoms was 3.5%. Time to symptom onset was 2 to 58 months (median, 26 months); most symptoms were self-limited and resolved within a few months. Grade 2 genitourinary symptoms were seen in 5.4% of patients at 3 years. Such symptoms occurred from 2 to 58 months (median, 28 months) after treatment.

Comparison with the Results of Other Treatment Modalities

Clinically localized prostate cancer is most often treated with radical prostatectomy, external photon beam irradiation (conformal or non-conformal), or managed conservatively, i. e., with watchful waiting or hormone therapy. The benefit of proton therapy in comparison with these alternative forms of management should ideally be tested in large randomized trials. The results of single-institutional series are usually not directly comparable because of unequal proportions of patients with known (and sometimes unknown) prognostic factors. Although, a randomized trial is currently being conducted comparing surgery with watchful waiting [27], no prospective randomized trials have been performed or are under way that would allow assessing the relative efficacy of different treatment modalities. In addition, besides costs and long duration, there are psychological and ethical problems with large randomized trials, in particular, when one arm employs a more advanced treatment modality.

In the absence of large randomized trials and considering the small probability that such trials will ever be conducted, one has to search for alternative methods to assess the strength and limitations of alternative treatment modalities. In large non-randomized series, including our own series, several independent prognostic factors for tumor control have been identified including clinical stage, Gleason score, and initial PSA level. Based on the results of 2 recently published studies, 1 a large single-institutional postsurgical series [12] and the other a pooled analysis of multi-institutional radiation therapy data [20], these prognostic factor categories can be used to predict the probability of 5-year freedom from biochemical recurrence in individual patients or a group of patients following surgery or external photon irradiation assuming that the distribution of prognostic factors is known.

This approach was used to obtain an unbiased estimation of the 5-year bNED rate after radical prostatectomy and external photon radiation therapy in the Loma Linda patients that were treated with proton irradiation for clinically localized prostate cancer. For patients in whom prognostic factors were known, the individual probability of remaining tumor-free after 5 years was calculated. These data were then used to estimate the 5-year bNED rate for the whole population as well as for individual subgroups. Table 3 compares the observed 5-year bNED after proton therapy with the evidence-based predictions for 5-year bNED for the proton treatment population assuming that these patients had been treated with either external photon beam radiation or radical prostatectomy alone. For the whole patient population the observed 5-year bNED was 82% whereas the predicted rates are 70% (95% CI, 60 to 80%) following surgery and 72% (95% CI, 63 to 82%) following external photon beam therapy. The advantageous tumor control rates after proton radiation are also observed in various prognostic subgroups.

In addition to improving tumor control, the second important goal of proton therapy is to minimize morbidity of normal tissue despite the high doses used to treat the tumor. Organs at risk and the typical late complications after radiation treatment for prostate cancer include rectum (chronic radiation proctitis, rectal bleeding), bladder (increased urinary frequency and urgency), and urethra (stricture). It has been demonstrated that with conventional radiation therapy techniques the incidence of severe complications rises considerably for doses above 70 Gy delivered to the prostate [23].

The estimation of the incidence of late complications in rectum, bladder, and urethra is more difficult compared to tumor control probability. This difficulty results from the large

	No of patients	Observed	5-year bNED Predicted after radical prostatectomy	5-year bNED Predicted after external photon irradiation
Initial PSA, ng/ml				
< 10	505	93	82 (72–92)	79 (71–88)
10.1–20	242	77	58 (48–68)	66 (55–80)
> 20	70	58	41 (31–51)	43 (32–58)
Clinical stage				
T1	228	83		78 (67–92)
T1a/b	24	80	69 (59–79)	
T1c	204	94	84 (74–94)	
T2	616	82		69 (60–79)
T2a	212	91	83 (73–92)	
T2b	203	78	58 (48–68)	
T2c	201	77	60 (50–70)	
T3	40	58	38 (28–48)	
Gleason score				
2–4	129	88	82 (72–91)	77 (67–89)
5–6	421	88	75 (65–85)	76 (68–85)
7–10	239	70	51 (41–61)	61 (50–74)
Total	901	82	70 (60–80)	71 (62–82)

Table 3. Comparison of predicted and observed 5-year bNED rates (%). Rates of no biochemical evidence of disease presented as percentage of patients (95% confidence interval).

Tabelle 3. Vergleich zwischen erwarteten und beobachteten Fünf-Jahres-Überlebensraten ohne biochemisches Rezidiv (PSA).

variability in the relationship between dose and partial organ volume that may be further confounded by patient and organ movements, different immobilization and shielding techniques, and non-uniformity in the use of late effect morbidity scales.

Schultheiss [19] performed a multivariate analysis of the incidence of late toxicity in the gastrointestinal (GI) and genitourinary (GU) tract in 712 patients with localized prostate cancer treated with non-conformal or conformal photon radiation techniques. Central axis doses in excess of 70 Gy were typically delivered with conformal radiation techniques. In this study, a modified RTOG morbidity scale for the rectum was used, which categorizes any rectal bleeding with 2 or fewer therapeutic coagulation procedures or pain requiring non-narcotic medication as Grade 2 GI toxicity, and rectal bleedings requiring transfusion or 3 or more coagulation procedures as Grade 3 toxicity. Compared with the original RTOG scale, this scale leads to a higher incidence of Grade 2 GI toxicity.

The study of Schultheiss [19] can be used to predict the risk of late GI morbidity in our patient group assuming they had been treated with conformal photon techniques alone. Using multivariate analysis, it was found that central axis dose was the strongest independent prognostic factor for the development of late complications. For a dose of 75.5 Gy, the 3-year incidence predicted by Schultheiss' model is 37% (95% CI, 26 to 46%) for late GI complications Grade > 2 and 5% (95% CI, 2 to 10%) for late GI complications Grade > 3, using the modified morbidity scale. In comparison, the observed 3-year incidence of late GI complications in the Loma Linda patients, which were treated to a dose of 74 to 75 CGE, was 21% for complications Grade 2 and < 1% for complications Grade 3. One should note that most of these Grade 2 occurrences were isolated episodes of bleeding, which were categorized as Grade 1 on the original RTOG morbidity scale.

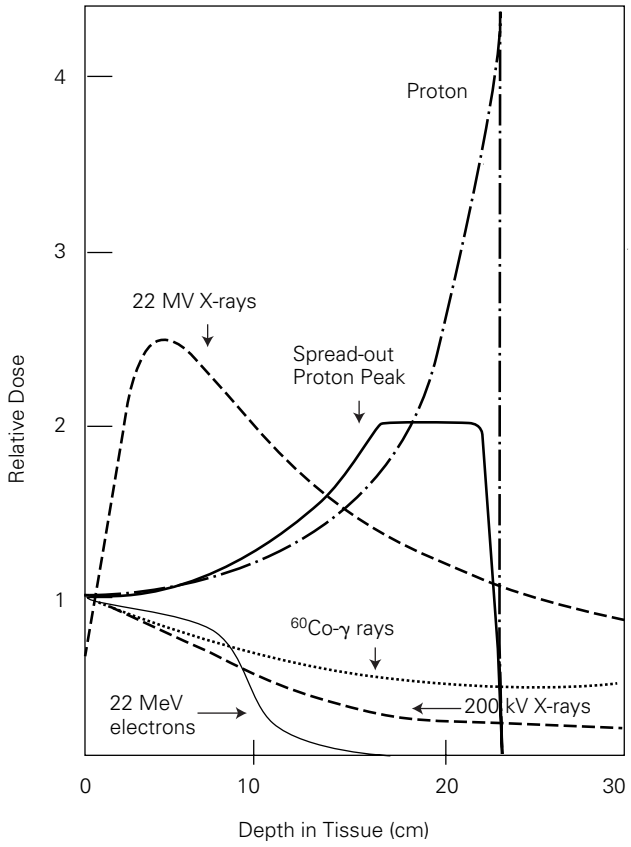

Figure 1. Dose distribution of protons as a function of penetration depth in tissue in comparison with other forms of ionizing radiation.

Abbildung 1. Tiefendosiskurven für Protonen im Vergleich zu verschiedenen Strahlenarten.

Future Developments

We are living in an era, which is characterized by great advances in technology, computer science, and molecular biology. These developments are likely to determine the future of cancer medicine in general and proton therapy of cancer in particular. At the same time, we experience an increasing awareness of cost effectiveness and the need to base therapeutic decisions on scientific evidence, which imposes a challenge in introducing new and potentially expensive equipment and methods into clinical practice. As financial resources for conducting expensive large center trials are becoming more and more limited, and patients are increasingly reluctant to be enrolled in randomized studies, in which one arm uses a more advanced treatment technology, we are challenged to develop innovative approaches to evaluate new technology critically.

Technological Perspectives

Active Beam Scanning and Intensity Modulated Proton Therapy: The present method of beam delivery used at LLUMC consists of a system of beam shaping objects such as

scattering foils, apertures, and tissue compensators, which are located in front of the patient. These passive devices spread the relatively narrow proton beam delivered to the treatment and shape the dose distribution in the patient as planned. The passive beam delivery system is simple, reliable and very effective for treating small- and moderate-sized tumors. On the other hand, active beam delivery involves sweeping the narrow proton beam through the target area in a controlled pattern while changing its energy and intensity [17]. This technique is also called intensity-modulated proton therapy (IMPT).

Design and manufacture of active beam delivery systems is either underway, or has been completed at several other accelerator facilities worldwide [17]. An active beam delivery system provides several clinical advantages. It allows to create very large, complex, irregularly shaped volumes and to reduce the dose to healthy tissues located in front of the target as compared to a passive beam delivery system. This is accomplished by depositing the dose in thin tissue layers. The dose for each layer can be configured in the desired 3-dimensional shape. The total treatment volume is composed of a stack of varyingly shaped layer matching the target. An active beam delivery system also eliminates the need for manufactured patient-specific devices and thus will reduce treatment costs. These additional capabilities will allow the development of new treatment protocols for patients with lymphomas, breast cancer, and other tumor sites.

Advances in Imaging and Treatment Planning Technology: Recent technologic advances in imaging technology, computerized image processing, and radiation therapy planning systems are likely to result in further improvements of the capability to conform high doses to the tumor volume in its entire 3D configuration while maximally excluding the surrounding normal tissues. Anatomic data for 3D treatment planning may be derived from modern imaging modalities such as CT, MRI, SPECT and PET. Since the information of these different imaging studies is usually complementary, methods are needed that provide a composite view of patient and tumor anatomy from different imaging modalities. These methods, which are referred to as image correlation, image registration or image fusion, are currently under active development [2], and first image correlation packages are already on the market. As image resolution and the power of image registration programs will increase in the future, it is likely that these methods will be increasingly used for accurate definition of tumor and normal tissue boundaries. The ultimate goal is to develop imaging techniques that combine functional and anatomical information and will allow delineating the boundaries of microscopic tumor infiltration into normal tissues.

Biological Perspectives

New Fractionation Schedules: The "fractionated" approach permits normal tissues included in the radiation field to repair the damage caused by radiation. In many cases, however, the tumor site is well demarcated from surrounding normal tissues and conformal radiation techniques such as proton therapy should allow physicians to deliver radiation in one or a few high-dose treatments with equal or enhanced effectiveness. Such short (hypofractionated) treatment schedules would be more convenient for patients, reduce the costs of proton treatments, and increase the treatment capacity of proton treatment centers.

At LLUMC the use of hypofractionated schedules has been successfully implemented for arteriovenous malformations of the brain, brain metastases, and recurrent malignant brain tumors. The possibility of applying hypofractionated proton boosts to patients with prostate cancer is currently being discussed.

Biological Response Modifiers: Many new biological treatments are currently under development that may be used as an adjunct to a proton therapy. Such therapies include the use of angiogenesis inhibitors, tumor vaccines, and immunotherapy, e. g., [13]. Previous studies with radiation sensitizers have been hampered by the increased systemic or treatment toxicity seen in normal tissues that were also exposed to therapeutic doses of radiation. In this respect, the greater sparing of normal tissues possible with proton radiation may lead to greater tolerance of bioreductive drugs.

Medical Perspectives

Future of Localized Therapeutic Modalities: While systemic chemotherapy is important to eradicate wide spread tumors such as malignant lymphomas and leukemias, surgery and radiation therapy remain the principal modalities in the treatment of localized tumors. Studies with animal models [18] as well as our experience with high-dose conformal radiation of prostate cancer support the hypothesis that localized therapeutic modalities have a curative potential in tumors that are still confined to their local or local-regional site at the time of treatment. With continuing improvement in screening and early detection of common cancers such as prostate cancer one can expect that more tumors will be detected when they are still confined. For example, data obtained from the Surveillance, Epidemiology, and End Results (SEER) program of the US National Cancer Institute show that prostate cancer incidence rates increased by 6.4% per year between 1983 and 1989, while an increase in the incidence rate of metastatic cancer at the time of diagnosis was seen [14]. This increase was attributed to the detection of early-stage disease. Projecting this trend on to other cancer sites, in which early detection programs have been instituted, e. g., breast cancer, one can anticipate that localized therapeutic modalities such as proton therapy will play an increasing role in the future.

Future Indications for Proton Therapy: One of the strengths of proton therapy is its versatility. With the availability of rotating beam delivery systems (gantries), high-energy proton beams, and active beam scanning techniques, the latter currently under development, there will be no limitations with respect to size and anatomical sites in which protons can be employed. In addition to the sites listed in Table 1, protocols for gynecologic cancers, gastrointestinal tumors and breast cancer are currently being developed at LLUMC. The Department of Radiation Medicine at LLUMC is also developing a program for the treatment of Parkinson's disease and intractable epilepsy with proton radiosurgery. Children, especially, will benefit from proton treatment. Radiation exposure of the brain and other tissues in young children can be associated with tissue damage and may lead to the development of radiation-induced cancers in later years. In this respect every measure that avoids the exposure of normal tissues to any radiation is of great value, and protons are likely to be increasingly used for the treatment of children with solid-tumor cancers.

Competing Technologies

Intensity-Modulated Photon Radiation Therapy (IMXRT): IMXRT represents the state-of-the-art photon beam therapy

[5]. This technology uses multileaf collimators to shape photon radiation beams. During radiation treatment, these leaves move across the radiation field thereby varying the beam intensity to achieve the desired dose distribution.

It has been argued that compared to proton therapy IMXRT can deliver the same or even better conformal doses to complex tumors at a small fraction of the capital cost a proton treatment center would require [15]. One should not forget, however, that with IMXRT the physical characteristic of the individual photon beams remains unchanged. Although the dose is redistributed favoring the dose delivered to the tumor, the total energy (or integral dose) deposited in the surrounding tissue remains the same. The apparently lower dose in the normal tissues can only be achieved by spreading the deposited radiation energy over a larger volume of normal tissue that receives radiation dose. This is of particular concern in the CNS of young children, where exposure of large volumes of tissue to a relatively low dose may lead to intellectual deficits. In addition, there is recent experimental evidence showing that doses less than 0.5 Gy may fail to induce cellular repair functions, which could lead to more toxicity than expected [11].

Both improvements in tumor control and reduction of treatment-associated complications will reduce the long-term costs associated with the management and economic impact of a failed cancer treatment and severe treatment-related complications. These benefits arising from high-quality patient care needs to be weighed against the additional costs associated with the implementation of proton radiation therapy.

References

1. Austin-Seymour M, Munzenrider J, Goitein M, et al. Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull. J Neurosurg 1989;70:13–7.
2. Cai J, Chu JC, Recine D, et al. CT and PET lung image registration and fusion in radiotherapy treatment planning using the chamfer-mathing method. Int J Radiat Oncol Biol Phys 1999;43:883–91.
3. Dahl O, Vikterlof KJ. Precision deep therapy with 200 to 250 kV roentgen rays and cobalt 60 gamma radiation; with special reference to perpendicular axial arc therapy. Acta Radiol 1939;188:71–80.
4. DeVries A, Munzenrider JE, Hedley-Whyte LT, et al. Die Rolle der Strahlentherapie in der Behandlung maligner Melanome. Strahlenther Onkol 1999;175:62–7.
5. Fraass BA, Kessler ML, McShan DL, et al. Optimization and clinical use of multisegment intensity-modulated radiation therapy for high-dose conformal therapy. Semin Radiat Oncol 1999;9:60–77.
6. Goitein M. Compensation for inhomogeneities in charged particle radiotherapy using computed tomography. Int J Radiat Oncol Biol Phys 1978;4:499–508.
7. Graffiuian S, Brahme A, Larsson B. Proton radiotherapy with the Uppsala cyclotron experience and plans. Strahlentherapie 1985;161:764–70.
8. Gragoudas ES, Goltein M, Koehler AM, et al. Proton irradiation of small choroidal malignant melanomas. Am J Ophthalmol 1977;83:665–73.
9. Hug EB, Loredo LN, Slater JD, et al. Proton radiation therapy for pediatric malignancies: status report. Strahlenther Onkol 1999;175:Suppl 2:89–91.
10. Hug ER, Slater ID. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. J Neurosurg 1999;91:432–9.
11. Joiner MC, Lambin P, Marples B. Adaptive response and induced resistance. CR Acad Sci III 1999;322:167–75.
12. Kattan MW, Eastham JA, Stapleton AM, et al. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. J Natl Cancer lnst 1998;90:766–71.
13. Lash CJ, Li AE, Rutland M, et al. Enhancement of the anti-tumour effects of the antivascular agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA) by combination with 5-hydroxytryptamine and bioreductive drugs. Br J Cancer 1998;78:439–45.
14. Lu-Yao OL, Greenberg ER. Changes in prostate cancer incidence and treatment in USA. Lancet 1994;343:251–4.
15. Mackie TR, Smith AR. Intensity-modulated conformal radiation therapy and 3-dimensional treatment planning will significantly reduce the need for therapeutic approaches with particles such as protons. Med Phys 1999;26:1185–7.
16. McAllister B, Archambeau JO, Nguyen MC, et al. Proton therapy for pediatric cranial tumors: preliminary report on treatment and disease-related morbidities. Int Radiat Oncol Biol Phys 1997;39:455–60.
17. Pedroni E, Bohringer T, Coray A, et al. Initial experience of using an active beam delivery technique at PSI. Strahlenther Onkol 1999;175:Suppl 2:18–20.
18. Peters LJ. The natural history of metastasis of syngeneic murine squamous carcinoma and the prognostic implications of primary tumour size and duration of growth. Br J Cancer 1975;32:366–72.
19. Schultheiss TE. Late GI and GU complications in the treatment of prostate cancer. Int Radiat Oncol Biol Phys 1997;37:3–11.
20. Shipley WU, Thames HD, Sandler HM, et al. Radiation therapy for clinically localized prostate cancer: a multi-institutional pooled analysis. JAMA 1999;281:1598–604.
21. Slater JD, Yonemoto LT, Rossi CJ Jr, et al. Conformal proton therapy for prostate carcinoma. Int J Radiat Oncol Biol Phys 1998;42:299–304.
22. Slater JM, Miller DW, Archambeau JO. Development of a hospital-based proton-beam treatment center. Int J Radiat Oncol Biol Phys 1988;14: 761–75.
23. Smit WG, Helle PA, van Putten WL, et al. Late radiation damage in prostate cancer patients treated by high dose external radiotherapy in relation to rectal dose. Int J Radiat Oncol Biol Phys 1990;18:23–9.
24. Tobias CA, Roberts JE, Lawrence ICH, et al. Irradiation hypophysectomy and related studies using 340-MeV protons and 190-MeV deuterons. Peaceful Uses Atomic Energy 1956;10:93–106.
25. Wilson RR. Radiological use of fast protons. Radiology 1946;47:487–91.
26. Wilson WR, Li AE, Cowan DS, et al. Enhancement of tumor radiation response by the antivascular agent 5,6-dimethylxanthenone-4-acetic acid. Int J Radiat Oncol Biol Phys 1998;42:905–8.
27. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial (PIVOT). Oncology 1997;11:1133–9.
28. Yonemoto LT, Slater JD, Friedrichsen E, et al. Phase I/II study of proton beam irradiation for the treatment of subfoveal choroidal neovascularization in age-related macular degeneration: treatment techniques and preliminary results. Int J Radiat Oncol Biol Phys 1996;36:867–71.
29. Yonemoto LT, Slater JD, Rossi CJ Jr, et al. Combined proton and photon conformal radiation therapy for locally advanced carcinoma of the prostate: preliminary results of a phase I/II study. Int J Radiat Oncol Biol Phys 1997;37:21–9.

Address for Correspondence: Reinhard W. Schulte, MD,
Department of Radiation Medicine, 11234 Anderson Street,
Loma Linda, CA 92354, USA,
Fon (+1/909) 558-4243, Fax -4083,
e-mail: rschulte@prolit.llu.edu