

Current Status of Radiotherapy With Proton and Light Ion Beams

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Several model studies have shown potential clinical advantages with charged particles (protons and light ions) compared with 3D-conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) in many disease sites. The newly developed intensity-modulated proton therapy (IMPT) often yields superior dose distributions to photon IMRT, with the added advantage of a significant reduction in the volume of healthy normal tissues exposed to low-to-medium doses. Initially, the major emphasis in clinical research for proton and light ion therapy was dose escalation for inherently radioresistant tumors, or for lesions adjacent to critical normal structures that constrained the dose that could be safely delivered with conventional x-ray therapy. Since the advent of IMRT the interest in particle therapy has gradually shifted toward protocols aimed at morbidity reduction. Lately the emphasis has mostly been placed on the potential for reduced risk of radiation-induced carcinogenesis with protons. Compared with 3D-CRT, a 2-fold increase has been theoretically estimated with the use of IMRT due to the larger integral volumes. In the pediatric setting, due to a higher inherent susceptibility of tissues, the risk could be significant, and the benefits of protons have been strongly emphasized in the literature. There is a significant expansion of particle therapy facilities around the world. Increasing public awareness of the potential benefits of particle therapy and wider accessibility for patients require that treating physicians stay abreast of the clinical indications of this radiotherapy modality. The article reviews the available literature for various disease sites in which particle therapy has traditionally been considered to offer clinical advantages and to highlight current lines of clinical research. The issue of radiation-induced second malignancies is examined in the light of the controversial epidemiological evidence available. The cost-effectiveness of particle therapy is also discussed. *Cancer* 2007;109:1227-38. © 2007 American Cancer Society.

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Charged particles (protons and light ions) have a finite range in tissues. The interaction probability to cause ionization increases as they lose velocity traversing through tissues, so that a peak of dose occurs at a depth proportional to the energy of each particle. Beyond this peak no further dose deposition occurs. This phenomenon was described by William Bragg over 100 years ago.¹ The dose peak may be 'spread out' to achieve a plateau of uniform dose to precisely cover the target while sparing adjacent normal structures. Passively scattered beams of a certain aperture can be produced by means of range-shifting modulators of variable thickness providing spread-out Bragg peaks (SOBP) for clinical use. The recent introduction of the spot scanning method represents a major advance in particle therapy.² In this method, small pencil beams of a certain

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energy deposit their peaks to obtain an exquisite 'dose-sculpting' of the target. The newly developed intensity-modulated proton therapy (IMPT), which can be delivered with the spot scanning method, has been shown to yield superior dose distributions to photon intensity-modulated radiotherapy (IMRT), with the added advantage of a significant reduction in the volume of healthy normal tissues exposed to low-to-medium doses.³

In spite of almost 43,000 patients treated with protons worldwide, there are still few published controlled clinical trials comparing protons and light ions to x-ray radiation therapy.⁴ There is a growing number of particle therapy facilities around the world.⁵ Heightened public awareness of the potential advantages of particle therapy may be the marketing drive for the development of these new facilities. It is hoped that the increased accessibility to this form of radiation therapy will allow comparative clinical trials to be performed so that the relative merits can be formally studied.

The dose delivered with particles is prescribed in Gray equivalents (GyE) or cobalt Gray equivalents (CGE) often used with protons. GyE and CGE are equal to the measured physical dose in Gray multiplied by the relative biological effectiveness (RBE) factor specific for the beam used. The RBE is the ratio of dose of radiation required to produce a certain biological effect with photons relative to the dose required to produce the same effect with another form of ionizing radiation such as protons and light ions. An RBE value of 1.1 is generally accepted for clinical use with proton beams.⁶ The RBE of carbon ions is difficult to calculate and for dose-reporting purposes a value of 3 is often utilized.⁷ In essence, carbon ion therapy attempts to capture the 'best of both worlds,' by exploiting the benefits of improved dose distributions, due to the presence of a defined Bragg peak and concomitantly taking advantage of their high RBE to increase the tumor control probability.

Pediatric Malignancies

The use of radiation therapy in children and adolescents is particularly challenging because of the potential long-term side effects. Depending on the sites of irradiation, patients may develop problems relating to growth, intelligence, cosmesis, endocrine function, fertility, and organ function. Radiation side effects become an even more serious concern for very young patients (age <3 years), whose tissues have been shown to be especially susceptible to radiation damage.⁸ Radiation carcinogenesis is another serious concern in children.

Comparative studies for proton-beam vs 3D-conformal radiotherapy (3D-CRT) vs IMRT for selected pediatric tumors have invariably found protons to deliver superior target dose coverage and sparing of normal structures. Proton therapy may improve treatment for a variety of pediatric malignancies including medulloblastoma and other central nervous system tumors, retinoblastoma, and sarcomas. In diseases for which lower doses and wider fields of radiotherapy are indicated, such as Wilms tumor, neuroblastoma, and Hodgkin disease, the role of protons is limited. Clinical trials of proton-beam radiation therapy for pediatric patients are currently in progress at several facilities around the world.

Central nervous system tumors

Radiotherapy plays a pivotal role in the management of many patients with central nervous system tumors, including medulloblastoma. In a recent study, St. Clair et al.⁹ compared standard photons, IMRT, and protons for craniospinal irradiation with a posterior fossa boost. Substantial normal tissue sparing was seen with protons. The dose to 90% of the cochlea was reduced from 101% with standard photons, to 33% with IMRT, and to 2% with protons. An example of this is illustrated in Figure 1. Dose to 50% of the heart volume was reduced from 72% with standard x-rays to 30% with IMRT and to 0.5% with protons. IMRT, however, exposed 50% of the volumes of lung and kidney to significantly higher doses than with conventional photon irradiation. Similar findings have been recently described by Lee et al.¹⁰ Yuh et al.¹¹ from Loma Linda University reported on the outcome of exclusive proton irradiation in young children with medulloblastoma. Treatment consisted of 36 CGE to the craniospinal axis followed by an 18 CGE boost to the posterior fossa. A significant reduction in normal tissue doses was achieved with protons, resulting in reduced treatment-related acute side effects such as esophagitis and nausea.

Retinoblastoma

Retinoblastoma is the most common primary ocular malignancy in childhood. In 20% to 30% of cases the disease is bilateral and associated with a germline mutation in the Rb tumor suppressor gene. Due to their genetic predisposition, survivors of hereditary retinoblastoma treated with radiation have been shown to have a high incidence of second malignancies, which is significantly increased in radiation-exposed tissues.¹²

Conventional external beam radiotherapy (EBRT) has been used for decades as an alternative to enucleation and as the primary treatment for extraocular

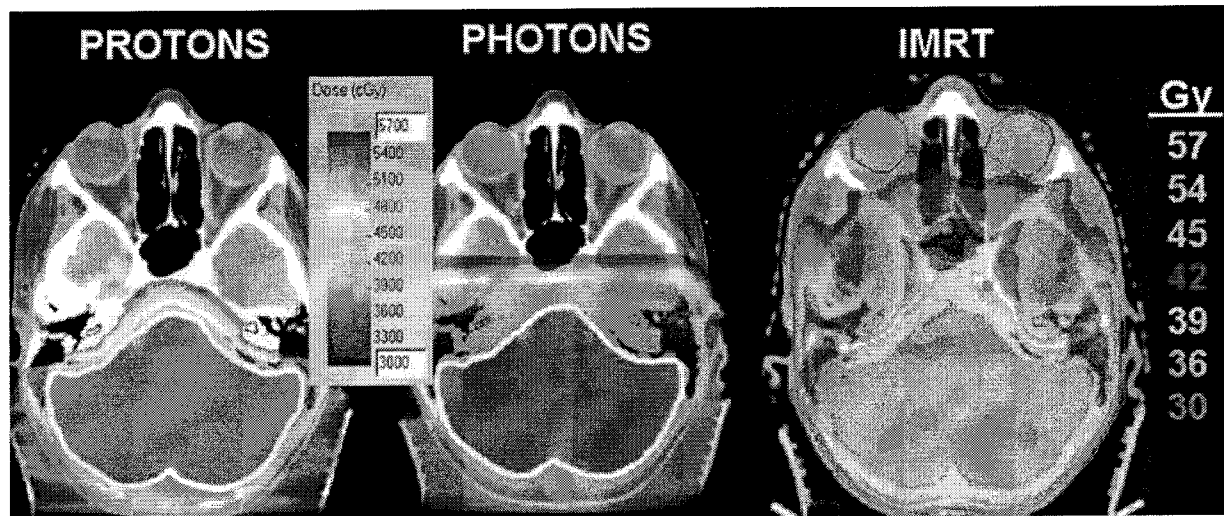


FIGURE 1. A comparison of dose distributions for treatment of the posterior fossa in a patient with medulloblastoma, using protons, photons, and intensity-modulated radiation therapy (IMRT). The cochleae are outlined in blue. Courtesy of Dr. Torunn Yock, Massachusetts General Hospital.

disease. Despite its documented ability to obtain local control, conventional EBRT causes orbital hypoplasia with poor cosmetic outcome, especially in children <6 months of age.^{13,14} The most devastating long-term side effect of EBRT, however, remains the induction of a second malignancy (generally sarcomas). In patients with hereditary retinoblastoma, this risk has been reported to be as high as 51% at 50 years.¹²

Lee et al.,¹⁰ in a comparative planning study, demonstrated that proton therapy provides superior target coverage with optimal sparing of orbital bone compared with 3D-CRT and IMRT. Retrospective research has indicated 5 Gy as a significant threshold for an increased risk of in-field sarcoma occurrence.¹³ The mean orbital bone volume exposed to 5 Gy was 10% for protons vs 25% for 3D-CRT electrons vs 41% for a single 3D lateral photon beam vs 69% for photon IMRT. Another comparative planning study showed that with a single proton beam and to a prescribed dose of 46 CGE to the gross tumor volume (GTV), the dose to sensitive structures was negligible.¹⁵ Therefore, proton-beam irradiation in retinoblastoma holds the potential to significantly reduce both poor cosmetic outcomes and radiation-induced malignancies.

Pediatric sarcomas

Sarcomas of bone and soft tissue are relatively common in the pediatric population and many children require moderate to high doses of radiation to achieve cure. Rhabdomyosarcoma is the most common soft-tissue sarcoma, frequently arising in the

head and neck and the genitourinary (GU) system. These sites are especially difficult to treat because of the numerous sensitive normal tissues surrounding the tumor as well as the very young patient age (most are <7 years old). Excellent results have been achieved with IMRT for head and neck rhabdomyosarcoma but further improvements may be possible with protons in certain cases.¹⁶ Yock et al.¹⁷ compared proton dosimetry to 3D-CRT photon plans (but not IMRT) for patients with orbital rhabdomyosarcoma and found that protons were superior because of reduced exposure to orbital structures, brain, and pituitary gland. In a treatment-planning comparison Lee et al.¹⁰ analyzed 3 cases of childhood pelvic sarcomas treated to doses ranging between 36 and 45 Gy. The single most important advantage found with the use of protons was the sparing of the ovaries. Unlike IMRT and 3D-CRT, a single proton beam had the ability to spare the ovaries completely with 0% of the volume receiving dose. This is of questionable clinical significance because ovarian function should remain intact as long as the dose is kept below 10 Gy. This is generally possible with IMRT and/or oophoropexy. No significant reduction was observed with the use of protons in terms of the amount of the pelvic bone or vertebrae exposed to ≥ 20 Gy, so bone growth is expected to be similar with protons and IMRT in these sample cases.

Whereas Ewing sarcoma and rhabdomyosarcoma can be successfully managed with radiotherapy doses in the 50–56 Gy range, unresectable osteosarcoma and nonrhabdomyosarcoma soft-tissue sarcomas have

not been controlled with similar radiation doses. There is evidence that these tumors could be cured if radiation dose-escalation were employed. A retrospective series patients with osteosarcoma showed local control of 78% for incompletely resected and 40% for unresected tumors with median doses up to 80 Gy. The majority of patients had received proton radiotherapy.¹⁸ It is plausible that with doses of 70 Gy or higher unresectable osteosarcoma and nonrhabdomyosarcoma soft-tissue sarcomas could be controlled with radiation. Protons are the most feasible means to achieve dose escalation to these levels.

Although doses of radiation used in most pediatric malignancies are not particularly high, integral doses with IMRT pose a concern, making proton irradiation particularly attractive in numerous clinical situations. The reduced integral dose to healthy nontarget tissues may lead to a reduction in the risk of radiation-induced malignancies over the lifetime of these patients. The issue of radiation-induced carcinogenesis will be discussed in more detail below.

Uveal Melanoma

Uveal melanoma is the most common primary ocular tumor. Historically, the primary treatment has been enucleation. Episcleral radioactive plaques, proton-beam irradiation, and helium ions have been proposed as an alternative to enucleation with the intent to preserve sight, although this is not always achievable due to the proximity of the optic nerve or fovea. Overall survival with proton-beam therapy has been shown to be comparable to enucleation series.¹⁹

The Massachusetts General Hospital (MGH) began treating uveal melanomas with protons in 1975. Gragoudas et al.²⁰ recently reported on their long-term outcomes. In a large series with a median follow-up of over 9 years, a 95% local control was observed. The overall eye-retention rate was reported as 84% at 15 years. Typically, a dose of 70 CGE was administered over 5 treatment sessions. Approximately 14% of patients had significant visual loss after therapy. Because of the exceptionally high local control rate, a randomized dose-reduction trial was conducted, decreasing the dose to 50 CGE in 5 sessions. Preliminary data at a median follow-up of 60 months indicate that local control and survival have not decreased, but no improvement in visual acuity has been observed.^{21,22}

Based on the assumption that the radioresistance of melanomas could be overcome by the higher linear energy transfer (LET) of heavier charged particles, a helium ion experience was conducted at

Berkeley.²³ Local control at 10 years was reported at 95.4% and considered comparable to that achievable with protons.²⁴

A large retrospective analysis from the Paul Scherrer Institut (PSI) reported excellent eye-retention outcomes, with an overall rate of 83.7 at 15 years.²⁵ After optimization of the treatment technique the 5-year eye-retention rate was raised from 97.1% to 100% in small tumors, from 86.7% to 99.7% in medium, and from 71.1% to 89.5% in large tumors.

To date, over 10,000 patients around the world with uveal melanoma have been treated with charged particles. With current techniques and appropriate patient selection a >98% local control rate can be expected.²⁴ On the other hand, long-term results of brachytherapy for intraocular melanomas suggest that this modality may provide equally satisfactory outcomes to particle therapy.²⁶

Sarcomas of the Base of Skull

The management of chordomas and chondrosarcomas of the base of skull is particularly challenging due to the proximity of dose-limiting critical structures.²⁷ Traditionally, surgery and conventional photon radiotherapy, with mean doses on the order of 60 Gy, have shown disappointing 5-year progression-free survival rates. The necessity to deliver higher doses of radiation in a very precise manner makes charged particles the treatment of choice for these tumors.

A large series of chondrosarcoma and chordomas of the skull base was treated at MGH.²⁸ A combination of proton and photon therapy to a median dose of 72.1 CGE was used. Local control rates for chondrosarcomas were 99% and 98% at 5 and 10 years, respectively. Patients with chordomas were found to have lower rates of local control in spite of similar doses, with 59% and 44% at 5 and 10 years, respectively. The temporal lobe damage rate was 13.2% at 5 years.²⁹ Similar encouraging outcomes have been reported from the Loma Linda group both in adult and pediatric patients.^{27,30}

Light ions have been extensively tested in the treatment of tumors of the base of skull. A large series using helium and neon ions comes from Berkeley.³¹ The 5-year local control rates were 78 and 63 for chondrosarcoma and chordoma, respectively. Radiation-induced complications occurred in 27% of patients.

Recently, the group at GSI, Germany, reported on a large series of patients treated with carbon ions, including 67 tumors of the base of skull.^{32,33} The prescribed median tumor dose was 60 GyE. Actuarial

3-year local control rates were 100% for chondrosarcomas and 81% for chordomas, which appear comparable to the published results with protons.

Paraspinal Tumors

Treatment of paraspinal tumors is complicated by the relatively low radiation tolerance of the spinal cord compared with the dose required for the treatment of sarcomas.

Primary and recurrent tumors of the skeletal axis have been treated at MGH with combined photon/proton irradiation with mean doses of 72.2 CGE for chondrosarcomas and 69.8 CGE for chordomas.³⁴ All patients with chondrosarcoma achieved and maintained local control at 5 years. Actuarial local control for chordoma was only 53% at 5 years, although a trend toward improved local control was observed for doses ≥ 77 Gy.

Weber et al.³⁵ recently performed a comparative treatment planning study between photon (IMRT) and proton (IMPT) intensity-modulated radiotherapy in paraspinal sarcomas. Tumor coverage was optimal and equally homogeneous with both IMRT and IMPT plans. The use of IMPT, however, leads to a substantial dose reduction to the organs at risk, thus allowing dose escalation to 92.9 CGE in all patients without exceeding normal-tissue constraints.

Shultz-Ertner et al.³⁶ reported on the feasibility of treating paraspinal tumors with a combination of photons and carbon ions. After surgical debulking, radiation treatment consisted of a combination of IMRT to a median dose of 50.4 Gy plus an 18 GyE carbon ion boost to the gross residual disease. Local control was reported in 8 of 9 patients with chordomas and chondrosarcomas.

Lung Tumors

Early-stage nonsmall-cell lung cancer (NSCLC) is optimally managed by surgery. Patients who are not operable for medical reasons are traditionally offered radiotherapy alone. A review of the outcomes of studies of conventional radiotherapy with definitive intent in early-stage NSCLC confirms poor local control with conventional doses.³⁷ Overall, with doses on the order of 60 to 70 Gy, approximately 41% local failure, 32% 3-year overall survival, and 43% disease-specific survival may be extrapolated. Attempts have recently been made to improve local control by means of dose escalation. One possible approach is through stereotactic hypofractionated x-ray radiotherapy.^{38,39} Particles have been extensively used in early-stage NSCLC and clinical data are available both for protons and for carbon ions.

Protons

The Loma Linda group recently reported on their experience with hypofractionated proton beam irradiation in stage I NSCLC.⁴⁰ Doses were 51 CGE in 10 fractions or 60 Gy CGE in 10 fractions (biologically equivalent to approximately 82 Gy). The 3-year local control rate and disease-specific survival were 74% and 72%, respectively, which compares favorably with published results with conventional radiotherapy. Local control rates were significantly better in T1 (≤ 3 cm) when compared with T2 (> 3 cm) (87% vs 49%) with a trend toward improved survival. No significant treatment-related toxicity was observed.

Similarly, the group from Chiba, Japan, with a total dose of 70–94 GyE delivered in 20 fractions, reported 2-year local control and overall survival rates as 80% and 84%, respectively.⁴¹ Local control at 2 years was significantly better in T1 (79%) vs T2 (60%). No serious acute toxicity was observed. However, grade 2 and 3 late pulmonary toxicity developed in 16% of patients, possibly due to tumor shrinkage (exposing more normal lung tissue) during the course of a relatively protracted treatment. Similar results have been published by the University of Tzukuuba.⁴²

Comparative clinical studies with similar fractionation and overall doses addressing the relative merits of proton therapy vs stereotactic or 3D-conformal x-ray radiotherapy in lung cancer are still unavailable. A model study with 10 stage I NSCLC patients planned with 3D-CRT and protons at doses of 66 Gy and 87.5 Gy has recently been reported.⁴³ Proton therapy was found to significantly spare the contralateral lung, heart, spinal cord, and esophagus. Based on these encouraging data, the M. D. Anderson group is going to conduct a Phase II clinical trial using image-guided proton radiotherapy for NSCLC with a total dose of 87.5 CGE in 2.5 CGE fractions (35 sessions) for stage I disease and 74 CGE with concurrent chemotherapy followed by adjuvant chemotherapy for stage III disease.

Carbon ions

Lung tumors often present with hypoxic radioresistant regions and may therefore represent an ideal setting for clinical trials with light ions. The literature on this topic is essentially limited to the Japanese experience.

The effectiveness of carbon ion therapy was substantiated by a small study of preoperative treatment in patients with locally advanced NSCLC.⁴⁴ The group from Chiba reported on a dose escalation trial with carbon ions for stage I NSCLC.⁴⁵ Initially, 18 fractions over 6 weeks were used. Doses were

escalated from 59.4 Gy E to 95.4 GyE in incremental steps of 10%. In a second stage, 9 fractions over 3 weeks were used with doses ranging from 68.4 GyE to 79.2 GyE in 5% increments. Overall, a 23.2% local recurrence rate was observed. However, with doses greater than 86.4 GyE at 18 fractions and greater than 72 GyE at 9 fractions, local control was 90% and 95%, respectively. Fifteen of 19 recurrences were 'in-field' but none of these developed in patients treated above 90 GyE in 18 fractions or 75.6 GyE in 9 fractions, suggesting that these were safe levels providing maximal local control.⁴⁶

Breast

Breast cancer has been proposed as a potential target for proton-beam therapy. Increased cardiac mortality after breast irradiation has been reported by some studies.^{47,48} Radiation-induced cardiac mortality has significantly decreased over time with advances in treatment techniques.^{49,50} The dose-volume relation for the myocardium is now relatively well established for a complication-free adjuvant irradiation of the breast.⁵¹ A recent retrospective study addressing morbidity in right- and left-sided breast cancer patients treated with breast conservation showed an increased incidence in coronary artery disease (CAD) and myocardial infarction in left-sided patients.⁵² CAD was significantly associated with the use of internal mammary node irradiation. Long-term overall survival, however, did not significantly differ between left- and right-sided irradiated patients.

The risk of radiation pneumonitis with current techniques is small and has been estimated to be on the order of approximately 1%.⁵³ In order to stay within safe dose/volume constraints for the organs at risk, breast irradiation may now be carried out with breathing-adapted techniques. Nevertheless, there may still be a category of breast cancer patients who may benefit from proton treatment, namely, node-positive left-sided breast managed with conservative surgery. In a model study IMRT and proton therapy were compared with conventional irradiation (x-rays and electrons) in patients to be treated to the left breast and regional lymph-nodes to a total dose of 50 Gy with conventional fractionation.⁵⁴ Target coverage was not improved with IMRT or protons. However, large differences in exposure to healthy tissues were found. The nontarget dose was approximately 3.8-fold higher for the IMRT and 2.5-fold higher for the conventional tangents, compared with the proton plan. It is noteworthy that the proton plan exposed the heart to virtually no dose. In a similar study, target coverage for IMRT and protons were comparable

but the IMRT plan delivered a higher mean dose to the heart (16 vs 6 Gy).⁵⁵

Recently, studies in advanced breast cancer using anthracycline or paclitaxel and trastuzumab have documented improved outcomes at the expense of a significantly increased cardiac toxicity.⁵⁶ Technical approaches that can minimize radiation exposure to the myocardium in patients at higher risk of cardiac morbidity are to be seriously considered.

Finally, the unique dosimetric features of protons have recently attracted interest in the field of partial breast irradiation.⁵⁷ In a Phase I/II trial a total dose of 32 CGE was delivered in 4 CGE fractions twice a day over 4 days. Follow-up is still too short for clinical/cosmetic evaluation.

Prostate

Dose-escalation studies, both retrospective and randomized, have shown a clear dose/response relation in prostate cancer.⁵⁸⁻⁶¹ The optimal dose with regard to local tumor control and normal tissue tolerance is still unclear. To evaluate the safety and to determine the recommendable dose of high-dose radiotherapy, the Radiation Therapy Oncology Group (RTOG) has conducted a dose escalation study (RTOG 9406) using 3D-CRT that indicates low late radiation-induced morbidity up to a dose of 78 Gy.⁶² Whether the improvements observed with dose escalation on local control and freedom from biochemical recurrence will necessarily translate into improved overall survival, however, is still to be seen.⁶³ The optimal modality to deliver high-dose irradiation is a matter of debate in the literature. Long-term follow-up data with use of high-dose IMRT with excellent biochemical control rates and optimal tolerance have recently been published.⁶⁴ IMRT, however, is known to result in larger integral doses, and worries of a consequent increased risk of induced secondary malignancy development have been expressed.^{65,66} The use of particle beams has been advocated as an alternative to IMRT to perform safe dose escalation in prostate cancer.

Protons

The MGH group reported on the use of protons as a boost technique for locally advanced prostate cancer.⁶⁷ A Phase III randomized trial in locally advanced (T3-T4) prostate cancer followed comparing conventional dose vs high dose by means of a proton boost.⁶⁸ Patients were randomized to receive either an additional 25.2 CGE by conformal proton-beam or an additional 16.8 Gy photon boost after a 4-field photon irradiation to 50.4 Gy. No hormonal therapy

was given. The proton boost technique consisted of a 160-MeV perineal approach in the lithotomy position, with the insertion of a rectal Lucite probe for correct alignment of the proton beam. This is undoubtedly an obsolete approach, and optimal rectal sparing is now typically achieved by a 2 lateral field technique. No overall difference in outcome was found between the 2 groups. In a subgroup analysis, however, poorly differentiated tumors (GPS 9 or 10) had improved local control with 94% and 84% in the proton boost arm and 64% and 19% in the photon only arm maintaining local control at 5 and 8 years, respectively. Toxicity was higher in the high-dose arm, likely due to the suboptimal proton boost treatment technique. In particular, the incidence of rectal bleeding was significantly higher in the proton boost arm (32% vs 12%, $P = .002$). Despite the increased morbidity in the high-dose arm, this study showed a significant clinical benefit with dose escalation in selected patient groups. A recent update from MGH with long-term follow-up for patients receiving 77.4 Gy reported an actuarial incidence of RTOG grade ≥ 2 gastrointestinal (GI) toxicity of 13% at 5 and 15 years.⁶⁹

Loma Linda University reported on their experience with proton-beam in prostate cancer.⁷⁰ Protons were either used exclusively to irradiate the prostate and seminal vesicles or as a boost after photon pelvic irradiation to 45 Gy. With a median follow-up of 62 months, the overall 5 and 8 years biochemical failure (bNED) rates were 75% and 73%, respectively. Acute GI and GU RTOG grade 3 or higher was $< 1\%$. Late RTOG grade 3 morbidity was 1% and grade 4 0.2%. No difference in toxicity was observed between those treated with mixed beam vs protons alone.

The experience of MGH and Loma Linda in proton-beam irradiation of prostate cancer led to the activation of a cooperative Phase III study (PROG 95-09).⁶¹ Patients with early-stage disease were randomized to receive an initial proton boost dose of 19.8 vs 28.8 CGE, followed by 50.4 Gy photon irradiation. At 5 years, freedom from bNED was 61.4% and 80.4% for the conventional and the high-dose levels, respectively. Only 1% of patients in the conventional-dose and 2% in the high-dose experienced RTOG acute grade 3 or higher urinary or rectal morbidity. Late RTOG grade 2 GI morbidity was 8% for the conventional-dose and 17% for the high-dose level ($P = .005$).

Although this trial validates the principle of dose escalation and the feasibility of high-dose proton-beam radiotherapy in prostate cancer, it was not designed to test whether this modality is more efficacious or cost-effective than other more readily

available techniques such as IMRT.⁷¹ A new dose escalation Phase I/II trial using 84.6 Gy with protons alone for early prostate cancer is now under way by the same 2 institutions. Again, the lack of comparison with IMRT will leave the issue of whether protons offer a measurable benefit unresolved.

A model study comparing several treatment plans including IMRT and IMPT for a prescription dose of 81 Gy confirmed that both techniques are successful in achieving target coverage while complying with the dose/volume constraints for the organ at risk (OAR).⁷² IMRT exposed nontarget tissues to a 1.7-fold increase in dose compared with IMPT. Thus, the only advantage of protons may be the small theoretical reduction in the risk of radiation-induced malignancies if the spot scanning method is used.

Light ions

Large experience with heavier particle beams in prostate cancer is limited to neutron therapy. Indeed, the higher RBE of neutrons and light ions offers potential radiobiological benefits in slow-growing and radioresistant tumors. Despite encouraging local control outcomes, neutron studies have shown high rates of adverse effects and their use has been largely discontinued.⁷³⁻⁷⁵

Due to their prominent Bragg peak, neon and carbon ion beams display exquisite dose distributions, similar to those of protons. The improved dose distributions to nontarget tissues may result in significantly lower normal tissue complication probabilities (NTCP) and reduced risk of radiation-induced malignancies compared with neutrons. Historical data on the use of neon ions in prostate radiotherapy comes from Berkeley.⁷⁶ The modern literature on light ions in prostate cancer is scarce and comes exclusively from Japan.

A Phase I/II dose escalation trial in T1b-T3 prostate cancer treated exclusively with carbon ions has recently been reported from Chiba.⁷⁷ The treatment schedule was 20 fractions 5 days a week with doses gradually increased from 54 GyE to 72 GyE in 10% increments. A recommended dose of 66 GyE emerged from this study. Analysis of the long-term outcome and toxicity data in a large group of patients has been reported recently.⁷⁸ No grade ≥ 3 toxicities were observed. Grade 2 late rectal toxicity was 1%. GU late grade 2 toxicity was 6%. Overall 5-year freedom from biochemical failure was 83.2%. Gleason score, initial prostate-specific antigen (PSA), and T stage were all independent predictors of bNED. Patients with initial PSA ≤ 20 ng/mL and GPS ≤ 7 had a 5-year bNED of 97.1%. In light of the favorable outcome with the adopted fractionation scheme

and minimal rate of late morbidity, the use of higher dose per fraction is currently under consideration.⁷⁸ Indeed, carbon-ion data compare favorably with published results for equivalent doses with x-rays, and the RBE for carbon ions may exceed 3.0.⁷ A recent update from the Chiba group has confirmed the feasibility and effectiveness of carbon ion therapy in prostate cancer.⁷⁹ Late grade 2 GI and GU morbidities were 2% and 5%, respectively. No grade 3 toxicities were observed. These outcomes compare favorably with the long-term published results from high-dose IMRT series.⁶⁴ A randomized trial comparing treatment outcomes of carbon-ion therapy with those from high-dose proton therapy and x-ray IMRT would be of great interest. Assessment instruments sensitive enough to capture other important elements of therapy outcome, such as health-related quality of life, ought to be used to appreciate subtle differences between treatments.

In a model study the Heidelberg group investigated the therapeutic potential of carbon-ion therapy in locally advanced prostate cancer. Due to their sharp dose fall-off, carbon-ion plans are particularly sensitive to organ motion and positioning uncertainties. Clinical evidence of improved local tumor control in locally advanced prostate cancer with the combination of photons and high LET neutrons is available.⁷³⁻⁷⁵ A combination of photon IMRT and carbon-ion boost to the GTV has thus been recommended as the most rational solution in gaining initial clinical experience.⁸⁰

Radiation-Induced Second Malignancies

The risk of secondary cancer induction after therapeutic irradiation is well recognized and documented. The potentially increased risk with IMRT, compared with conventional 3D-CRT, and the purported benefit of protons has recently drawn significant attention in the literature.

The risk of second malignancy induction is strongly dependent on the RBE of the radiation used. After fast neutron therapy, the risk of secondary cancer induction has been estimated to be approximately 10–20 times greater than after photon therapy.⁸¹ Carbon ions have an estimated RBE similar to neutrons. However, this risk estimate may be reduced by a factor of at least 3 due to the decreased integral dose.

On theoretical grounds, proton-beam therapy (RBE 1.1) carries a lower risk (by a factor of 3) of secondary cancer induction relative to photons due to the significant reduction of integral dose achievable through their superior physical properties. However,

an inherent problem of many current proton machines is that they employ passive modulation to produce a field size large enough for therapy. In this case, neutron scatter is produced, which has been estimated to result in effective dose to the patient that can be significantly higher than that characteristic of IMRT.⁸² This, however, is a rather controversial issue and more dosimetric studies on anthropomorphic phantoms are warranted. In order to overcome the problem of neutron contamination in proton therapy and to fully exploit the potential for second malignancy reduction the use of spot scanning has been proposed.⁸³

Children are particularly susceptible to the carcinogenic effect of radiation due to the increased cell turnover associated with growth and development. In a recent report, Gold et al.⁸⁴ updated the results of an earlier study in which a large cohort of children treated with radiation were followed to establish the nature and incidence of second malignancies. Actuarial survival at 30 years was 80% for all patients; 8.3% of patients developed a second cancer. Most occurred within the treatment field, with latency periods between 3.8 and 31.8 years (median, 15.5 years). The cumulative risk of second cancer was 13% at 30 years. Despite the high risk of second cancer, the associated mortality appears relatively low, with the overwhelming cause of death being recurrence of the original disease. A radiation dose effect for secondary sarcomas has been shown by numerous studies.⁸⁵⁻⁸⁷ Whereas the vast majority of radiation-induced tumors occur in tissues exposed to high doses, there is no threshold for this effect, so that low doses of radiation will also confer risk, albeit much smaller.

The advent of IMRT has raised a number of additional issues in pediatric radiotherapy, namely, the larger integral volume at low doses and leakage from the multileaf collimator (MLC). Leakage from MLCs is known to be on the order of 1% to 3%, and when large numbers of monitor units are prescribed for IMRT plans a higher total body exposure may result. Some technical measures to mitigate the problem of leakage radiation during IMRT have been proposed, such as increased shielding in the treatment head, or the removal of the flattening filter, which is not needed in a linear accelerator dedicated to IMRT.⁸²

Miralbell et al.⁸⁸ estimated the risk of second malignancy comparing treatment plans for a case of rhabdomyosarcoma of the paranasal sinus and for a case of medulloblastoma using 3D-CRT, IMRT, and proton beam irradiation. The expected risk of second malignancies was significantly reduced with protons by 2-fold for the rhabdomyosarcoma case and by

8- to 15-fold for the medulloblastoma. However, a pencil scanning beam must be used in order to minimize secondary neutron whole-body exposure.⁸³

The issue of second malignancy development in adults is of less concern but a small risk does exist. Retrospective analyses of epidemiologic data of second malignancies have been conducted, with conflicting results. For prostate irradiation, some studies indicate no increased risk of second cancers.^{89,90} Others have shown a significant association between irradiation and subsequent malignancy.⁹¹ In absolute terms, the number of second malignancies is definitely low (approximately 1% for long-term survivors), despite the relatively high hazard ratios reported. From a theoretical point of view, with the transition from conventional radiation therapy to 3D-CRT and the consequent reduction in normal tissue exposure a lower risk may be expected. The recent move to IMRT, with the larger volumes of normal tissues exposed to low-dose radiation and the total-body exposure due to leakage radiation and neutron contamination at high energies may result in an increase of second malignancies.^{65,66}

Cost-Effectiveness of Particle Therapy

Proton therapy is considerably more expensive than x-ray therapy.⁹² Proton therapy has been estimated to have a 1.5- to 3-fold increment in cost with respect to a similar accessory set-up with x-rays.⁹³ This broad range is a function of several factors including the number of patients treated per year, number of treatment rooms, and number of gantries. Goitein and Jermann⁹⁴ estimated that the current ratio of costs between protons and x-rays is approximately 2.4. The cost increase factor of 1.5 has been estimated to be appropriate where the initial capital investment is free of charge, the facility has a full schedule of patients for 14 hours a day, and operates with at least 3 gantries. The cost of light ions is estimated to be at least 3 times higher than that of protons and approximately 8 times higher than x-rays.⁹⁵

The peer-reviewed literature contains little evidence on the cost-effectiveness of proton or light ion radiotherapy.^{96,97} Cost-effectiveness must also take into account any proven clinical benefits of particle therapy. In a recent cost analysis of proton therapy in childhood medulloblastoma, proton-beam irradiation was considered to be more cost-effective than conventional photon irradiation.⁹⁸ The reduction in overall costs predicted in that study derives from the controversial claim that proton beam therapy will be associated with a reduced the risk of growth hormone deficiency and decreased intelligence quotient.

Economic evaluations of proton-beam therapy in breast cancer have concluded that it can be cost-effective in well-selected patient populations for whom the reduction in cardiac toxicity and mortality offered by protons translates into a significant gain in cost and quality-adjusted life years.^{99,100} The cost-effectiveness of proton therapy in prostate cancer has been the subject of a Swedish analysis.¹⁰¹ Based on a series of assumptions (including direct reduced mortality through dose escalation and reduced side effects), proton therapy has been deemed cost-effective in prostate cancer patients with longer life-expectancy and poorer prognostic factors.

REFERENCES

1. Brown A, Suit H. The centenary of the discovery of the Bragg peak. *Radiother Oncol.* 2004;73:265-268.
2. Lomax AJ, Bohringer T, Bolsi A, et al. Treatment planning and verification of proton therapy using spot scanning: initial experiences. *Med Phys.* 2004;31:3150-3157.
3. Lomax AJ, Pedroni E, Rutz H, et al. The clinical potential of intensity modulated proton therapy. *Z Med Phys.* 2004;14:147-152.
4. Glimelius B, Ask A, Bjelkengren G, et al. Number of patients potentially eligible for proton therapy. *Acta Oncol.* 2005;44:836-849.
5. Jones B. The case for particle therapy. *Br J Radiol.* 2006;79:24-31.
6. Paganetti H. Interpretation of proton relative biological effectiveness using lesion induction, lesion repair, and cellular dose distribution. *Med Phys.* 2005;32:2548-2556.
7. Kanai T, Matsufuji N, Miyamoto T, et al. Examination of GyE system for HIMAC carbon therapy. *Int J Radiat Oncol Biol Phys.* 2006;64:650-656.
8. Kiltie AE, Lashford LS, Gattamaneni HR. Survival and late effects in medulloblastoma patients treated with craniospinal irradiation under three years old. *Med Pediatr Oncol.* 1997;28:348-354.
9. St. Clair W, Adams JA, Bues M, et al. Advantage of protons compared to conventional x-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. *Int J Radiat Oncol Biol Phys.* 2004;58:727-734.
10. Lee CT, Bilton SD, Famiglietti RM, et al. Treatment planning with protons for pediatric retinoblastoma, medulloblastoma, and pelvic sarcoma: how do protons compare with other conformal techniques? *Int J Radiat Oncol Biol Phys.* 2005;63:362-372.
11. Yuh GE, Loredi LN, Yonemoto LT, et al. Reducing toxicity from craniospinal irradiation: using proton beams to treat medulloblastoma in young children. *Cancer J.* 2004;10:386-390.
12. Wong FL, Boice JD Jr, Abramson DH, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *JAMA.* 1997;278:1262-1267.
13. Kaste SC, Chen G, Fontanesi J, et al. Orbital development in long-term survivors of retinoblastoma. *J Clin Oncol.* 1997;15:1183-1189.
14. Imhof SM, Mourits MP, Hofman P, et al. Quantification of orbital and mid-facial growth retardation after megavoltage external beam irradiation in children with retinoblastoma. *Ophthalmology.* 1996;103:263-268.

15. Krengli M, Hug EB, Adams JA, et al. Proton radiation therapy for retinoblastoma: comparison of various intraocular tumor locations and beam arrangements. *Int J Radiat Oncol Biol Phys.* 2005;61:583-593.
16. Wolden SL, Wexler LH, Kraus DH, et al. Intensity-modulated radiotherapy for head-and-neck rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys.* 2005;61:1432-1438.
17. Yock T, Schneider R, Friedmann A, et al. Proton radiotherapy for orbital rhabdomyosarcoma: clinical outcome and a dosimetric comparison with photons. *Int J Radiat Oncol Biol Phys.* 2005;63:1161-1168.
18. Delaney TE, Park L, Goldberg SI, et al. Radiotherapy for local control of osteosarcoma. *Int J Radiat Oncol Biol Phys.* 2005;61:492-498.
19. Seddon JM, Gragoudas ES, Egan KM, et al. Relative survival rates after alternative therapies for uveal melanoma. *Ophthalmology.* 1990;97:769-777.
20. Gragoudas E, Li W, Goitein M, et al. Evidence-based estimates of outcome in patients irradiated for intraocular melanoma. *Arch Ophthalmol.* 2002;120:1665-1671.
21. Gragoudas ES, Marie LA. Uveal melanoma: proton beam irradiation. *Ophthalmol Clin North Am.* 2005;18:111-118, ix.
22. Gragoudas ES. A randomized, controlled trial of varying radiation doses in the treatment of choroidal melanoma. *Trans Am Ophthalmol Soc.* 1998;96:691-720.
23. Char DH, Kroll SM, Castro J. Ten-year follow-up of helium ion therapy for uveal melanoma. *Am J Ophthalmol.* 1998;125:81-89.
24. Char DH, Phillips T, Daftari I. Proton teletherapy of uveal melanoma. *Int Ophthalmol Clin.* 2006;46:41-49.
25. Egger E, Zografos L, Schalenbourg A, et al. Eye retention after proton beam radiotherapy for uveal melanoma. *Int J Radiat Oncol Biol Phys.* 2003;55:867-880.
26. Wilson MW, Hungerford JL. Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma. *Ophthalmology.* 1999;106:1579-1587.
27. Hug EB, Loredano LN, Slater JD, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg.* 1999;91:432-439.
28. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. *Strahlenther Onkol.* 1999;175(Suppl 2):57-63.
29. Santoni R, Liebsch N, Finkelstein DM, et al. Temporal lobe (TL) damage following surgery and high-dose photon and proton irradiation in 96 patients affected by chordomas and chondrosarcomas of the base of the skull. *Int J Radiat Oncol Biol Phys.* 1998;41:59-68.
30. Hug EB, Sweeney RA, Nurre PM, et al. Proton radiotherapy in management of pediatric base of skull tumors. *Int J Radiat Oncol Biol Phys.* 2002;52:1017-1024.
31. Castro JR, Linstadt DE, Bahary JP, et al. Experience in charged particle irradiation of tumors of the skull base: 1977-1992. *Int J Radiat Oncol Biol Phys.* 1994;29:647-655.
32. Schulz-Ertner D, Nikoghosyan A, Thilmann C, et al. Results of carbon ion radiotherapy in 152 patients. *Int J Radiat Oncol Biol Phys.* 2004;58:631-640.
33. Schulz-Ertner D, Nikoghosyan A, Thilmann C, et al. Carbon ion radiotherapy for chordomas and low-grade chondrosarcomas of the skull base. Results in 67 patients. *Strahlenther Onkol.* 2003;179:598-605.
34. Hug EB, Fitzek MM, Liebsch NJ, et al. Locally challenging osteo- and chondrogenic tumors of the axial skeleton: results of combined proton and photon radiation therapy using three-dimensional treatment planning. *Int J Radiat Oncol Biol Phys.* 1995;31:467-476.
35. Weber DC, Trofimov AV, Delaney TE, et al. A treatment planning comparison of intensity modulated photon and proton therapy for paraspinal sarcomas. *Int J Radiat Oncol Biol Phys.* 2004;58:1596-1606.
36. Schulz-Ertner D, Nikoghosyan A, Dindinger B, et al. Treatment planning intercomparison for spinal chordomas using intensity-modulated photon radiation therapy (IMRT) and carbon ions. *Phys Med Biol.* 2003;48:2617-2631.
37. Zimmermann FB, Bamberg M, Molls M, et al. Radiation therapy alone in early stage non-small cell lung cancer. *Semin Surg Oncol.* 2003;21:91-97.
38. Zimmermann FB, Geinitz H, Schill S, et al. Stereotactic hypofractionated radiation therapy for stage I non-small cell lung cancer. *Lung Cancer.* 2005;48:107-114.
39. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest.* 2003;124:1946-1955.
40. Bush DA, Slater JD, Bonnet R, et al. Proton-beam radiotherapy for early-stage lung cancer. *Chest.* 1999;116:1313-1319.
41. Nihei K, Ogino T, Ishikura S, et al. High-dose proton beam therapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2006;65:107-111.
42. Shioyama Y, Tokuyue K, Okumura T, et al. Clinical evaluation of proton radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2003;56:7-13.
43. Chang JY, Liu HH, Komaki R. Intensity modulated radiation therapy and proton radiotherapy for non-small cell lung cancer. *Curr Oncol Rep.* 2005;7:255-259.
44. Yamamoto N, Miyamoto T, Nishimura H, et al. Preoperative carbon ion radiotherapy for non-small cell lung cancer with chest wall invasion—pathological findings concerning tumor response and radiation induced lung injury in the resected organs. *Lung Cancer.* 2003;42:87-95.
45. Miyamoto T, Yamamoto N, Nishimura H, et al. Carbon ion radiotherapy for stage I non-small cell lung cancer. *Radiother Oncol.* 2003;66:127-140.
46. Koto M, Miyamoto T, Yamamoto N, et al. Local control and recurrence of stage I non-small cell lung cancer after carbon ion radiotherapy. *Radiother Oncol.* 2004;71:147-156.
47. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet.* 2000;355:1757-1770.
48. Gyenes G, Rutqvist LE, Liedberg A, et al. Long-term cardiac morbidity and mortality in a randomized trial of pre- and postoperative radiation therapy versus surgery alone in primary breast cancer. *Radiother Oncol.* 1998;48:185-190.
49. Giordano SH, Kuo YF, Freeman JL, et al. Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst.* 2005;97:419-424.
50. Patt DA, Goodwin JS, Kuo YF, et al. Cardiac morbidity of adjuvant radiotherapy for breast cancer. *J Clin Oncol.* 2005;23:7475-7482.
51. Gagliardi G, Lax I, Soderstrom S, et al. Prediction of excess risk of long-term cardiac mortality after radiotherapy of stage I breast cancer. *Radiother Oncol.* 1998;46:63-71.
52. Harris EE, Correa C, Hwang WT, et al. Late cardiac mortality and morbidity in early-stage breast cancer patients after

- breast-conservation treatment. *J Clin Oncol*. 2006;24:4100-4106.
53. Minor GI, Yashar CM, Spanos WJ Jr, et al. The relationship of radiation pneumonitis to treated lung volume in breast conservation therapy. *Breast J*. 2006;12:48-52.
 54. Johansson J, Isacson U, Lindman H, et al. Node-positive left-sided breast cancer patients after breast-conserving surgery: potential outcomes of radiotherapy modalities and techniques. *Radiother Oncol*. 2002;65:89-98.
 55. Lomax AJ, Cella L, Weber D, et al. Potential role of intensity-modulated photons and protons in the treatment of the breast and regional nodes. *Int J Radiat Oncol Biol Phys*. 2003;55:785-792.
 56. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol*. 2002;20:1215-1221.
 57. Taghian AG, Kozak KR, Katz A, et al. Accelerated partial breast irradiation using proton beams: initial dosimetric experience. *Int J Radiat Oncol Biol Phys*. 2006;65:1404-1410.
 58. Hanks GE, Hanlon AL, Epstein B, et al. Dose response in prostate cancer with 8-12 years' follow-up. *Int J Radiat Oncol Biol Phys*. 2002;54:427-435.
 59. Pollack A, Zagars GK, Starckschall G, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys*. 2002;53:1097-1105.
 60. Zelefsky MJ, Fuks Z, Hunt M, et al. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys*. 2002;53:1111-1116.
 61. Zietman AL, Desilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA*. 2005;294:1233-1239.
 62. Michalski JM, Winter K, Purdy JA, et al. Toxicity after three-dimensional radiotherapy for prostate cancer on RTOG 9406 dose Level V. *Int J Radiat Oncol Biol Phys*. 2005;62:706-713.
 63. Morris DE, Emami B, Mauch PM, et al. Evidence-based review of three-dimensional conformal radiotherapy for localized prostate cancer: an ASTRO outcomes initiative. *Int J Radiat Oncol Biol Phys*. 2005;62:3-19.
 64. Zelefsky MJ, Chan H, Hunt M, et al. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urol*. 2006;176:1415-1419.
 65. Hall EJ, Wu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys*. 2003;56:83-88.
 66. Kry SE, Salehpour M, Followill DS, et al. The calculated risk of fatal secondary malignancies from intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2005;62:1195-11203.
 67. Duttenhaver JR, Shipley WU, Perrone T, et al. Protons or megavoltage x-rays as boost therapy for patients irradiated for localized prostatic carcinoma. An early phase I/II comparison. *Cancer*. 1983;51:1599-1604.
 68. Shipley WU, Verhey LJ, Munzenrider JE, et al. Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. *Int J Radiat Oncol Biol Phys*. 1995;32:3-12.
 69. Gardner BG, Zietman AL, Shipley WU, et al. Late normal tissue sequelae in the second decade after high dose radiation therapy with combined photons and conformal protons for locally advanced prostate cancer. *J Urol*. 2002;167:123-126.
 70. Slater JD, Rossi CJ Jr, Yonemoto LT, et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. *Int J Radiat Oncol Biol Phys*. 2004;59:348-352.
 71. Zelefsky MJ, Fuks Z, Happersett L, et al. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. *Radiother Oncol*. 2000;55:241-249.
 72. Cella L, Lomax A, Miralbell R. New techniques in hadrontherapy: intensity modulated proton beams. *Phys Med*. 2001;17(Suppl 1):100-102.
 73. Griffin TW, Krall JM, Russell KJ, et al. Fast neutron irradiation of locally advanced prostate cancer. *Semin Oncol*. 1988;15:359-365.
 74. Laramore GE, Krall JM, Thomas FJ, et al. Fast neutron radiotherapy for locally advanced prostate cancer. Final report of Radiation Therapy Oncology Group randomized clinical trial. *Am J Clin Oncol*. 1993;16:164-167.
 75. Russell KJ, Caplan RJ, Laramore GE, et al. Photon versus fast neutron external beam radiotherapy in the treatment of locally advanced prostate cancer: results of a randomized prospective trial. *Int J Radiat Oncol Biol Phys*. 1994;28:47-54.
 76. Linstadt DE, Castro JR, Phillips TL. Neon ion radiotherapy: results of the phase I/II clinical trial. *Int J Radiat Oncol Biol Phys*. 1991;20:761-769.
 77. Akakura K, Tsujii H, Morita S, et al. Phase I/II clinical trials of carbon ion therapy for prostate cancer. *Prostate*. 2004;58:252-258.
 78. Tsuji H, Yanagi T, Ishikawa H, et al. Hypofractionated radiotherapy with carbon ion beams for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2005;63:1153-1160.
 79. Ishikawa H, Tsuji H, Kamada T, et al. Carbon ion radiation therapy for prostate cancer: results of a prospective phase II study. *Radiother Oncol*. 2006;81:57-64.
 80. Nikoghosyan A, Schulz-Ertmer D, Didinger B, et al. Evaluation of therapeutic potential of heavy ion therapy for patients with locally advanced prostate cancer. *Int J Radiat Oncol Biol Phys*. 2004;58:89-97.
 81. Engels H, Wambersie A. Relative biological effectiveness of neutrons for cancer induction and other late effects: a review of radiobiological data. *Recent Results Cancer Res*. 1998;150:54-87.
 82. Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. *Int J Radiat Oncol Biol Phys*. 2006;65:1-7.
 83. Schneider U, Agosteo S, Pedroni E, et al. Secondary neutron dose during proton therapy using spot scanning. *Int J Radiat Oncol Biol Phys*. 2002;53:244-251.
 84. Gold DG, Neglia JB, Potish RA, et al. Second neoplasms following megavoltage radiation for pediatric tumors. *Cancer*. 2004;100:212-213.
 85. Tucker MA, D'Angio GJ, Boice JD Jr, et al. Bone sarcomas linked to radiotherapy and chemotherapy in children. *N Engl J Med*. 1987;317:588-593.
 86. Koshy M, Paulino AC, Mai WY, et al. Radiation-induced osteosarcomas in the pediatric population. *Int J Radiat Oncol Biol Phys*. 2005;63:1169-1174.
 87. Kuttesch JF Jr, Wexler LH, Marcus RB, et al. Second malignancies after Ewing's sarcoma: radiation dose-dependency of secondary sarcomas. *J Clin Oncol*. 1996;14:2818-2825.

88. Miralbell R, Lomax A, Cella L, Schneider U. Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. *Int J Radiat Oncol Biol Phys.* 2002;54:824-829.
89. Movsas B, Hanlon AL, Pinover W, et al. Is there an increased risk of second primaries following prostate irradiation? *Int J Radiat Oncol Biol Phys.* 1998;41:251-255.
90. Chrouser K, Leibovich B, Bergstralh E, et al. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. *J Urol.* 2005;174:107-110.
91. Brenner DJ, Curtis RE, Hall EJ, et al. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer.* 2000;88:398-406.
92. Lundkvist J, Ekman M, Ericsson SR, et al. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. *Acta Oncol.* 2005;44:850-861.
93. Suit HD. Protons to replace photons in external beam radiation therapy? *Clin Oncol (R Coll Radiol).* 2003;15:S29-S31.
94. Goitein M, Jermann M. The relative costs of proton and x-ray radiation therapy. *Clin Oncol (R Coll Radiol).* 2003;15:S37-S50.
95. Turesson I, Johansson KA, Mattsson S. The potential of proton and light ion beams in radiotherapy. *Acta Oncol.* 2003;42:107-114.
96. Dahl O. Protons. A step forward or perhaps only more expensive radiation therapy? *Acta Oncol.* 2005;44:798-800.
97. Munro AJ. Particle matters. *Br J Radiol.* 2006;79:276-277.
98. Lundkvist J, Ekman M, Ericsson SR, et al. Cost-effectiveness of proton radiation in the treatment of childhood medulloblastoma. *Cancer.* 2005;103:793-801.
99. Lundkvist J, Ekman M, Ericsson SR, et al. Economic evaluation of proton radiation therapy in the treatment of breast cancer. *Radiother Oncol.* 2005;75:179-185.
100. Bjork-Eriksson T, Glimelius B. The potential of proton beam radiation therapy in breast cancer. *Acta Oncol.* 2005;44:884-889.
101. Johansson B, Ridderheim M, Glimelius B. The potential of proton beam radiation therapy in prostate cancer, other urological cancers and gynaecological cancers. *Acta Oncol.* 2005;44:890-895.