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Physical and Biological Basis of Proton and of Carbon Ion Radiation Therapy and Clinical Outcome Data

Herman Suit*, Thomas F. Delaney† and Alexei Trofimov‡
Department of Radiation Oncology,
Massachusetts General Hospital and Harvard Medical School,
Boston, MA, USA
**hsuit@partners.org*
†tdelaney@partners.org
‡atrofimov@partners.org

There is a clear basis in physics for the clinical use of proton and carbon beams in radiation therapy, namely, the finite range of the particle beam. The range is dependent on the beam initial energy, density and atomic composition of tissues along the beam path. Beams can be designed that penetrate to the required depth and deliver a uniform biologically effective dose across the depth of interest. The yield is a superior dose distribution relative to photon beams. There is a *potential* clinical advantage from the high linear energy transfer (LET) characteristics of carbon beams. This is based on a lower oxygen enhancement ratio (OER) and a flatter age response function. However, due to uncertainties relating OER with relative biological effectiveness (RBE), there is no clinical evidence to date that carbon ion beams have an advantage over proton beams. We strongly support performance Phase III clinical trials of protons *vs* carbon ion beams designed to feature a single variable, LET. Dose fractionation would be identical in both arms and dose distribution would be similar for the sites to be tested. For sites for which the carbon beam has a demonstrated important advantage in comparative treatment planning due to the narrower penumbra would not be selected for the clinical trials.

Keywords: Protons; carbon ions; beams; radiation therapy.

1. Introduction

The intent in implementation of a new radiation treatment method is to increase the probability of eradication of the irradiated tumor with no increase or preferably a lesser risk of treatment-related morbidity. This goal has been realized in multiple steps throughout the history of radiation oncology by technical advances that have provided progressively improving distributions of the dose. In parallel, major clinical gains have been made by combining radiation with other treatment modalities, viz. surgery, chemicals and biological/genetic agents.

At present, high interest is directed to the possibility of important gains in curative radiation therapy by moving from x-ray to proton and carbon ion beams. This is evident from the 61,112 patients treated by protons and the 5342 patients by carbon ion beams as of March 2009 (M. Jermann,[a] personal communication, 2009). These treatments have been delivered at 26 proton and 3 carbon ion therapy centers. Further, many proton and carbon ion centers are being planned or under construction. Here, we assess the relative merits of these two particle beams for radiation therapy by considering some of the relevant physics, radiation biology and clinical outcome data. This is not based on data from clinical trials, as there are none.

There have been earlier reviews of particle beam radiation therapy, such as Refs. 8, 17, 26, 50, 63 and 65.

[a]M. Jermann is the Secretary of the Particle Therapy Co-operative Oncology Group. See also his website, PTCOG.web.psi.ch.

2. Physics

2.1. *General considerations*

The physical basis for the enthusiasm for ^{1}H and ^{12}C therapy is the finite range of protons and carbon ions. Thus, the radiation dose is near zero for all tissues deep to the target for each beam path of ^{1}H beams, but not quite so low for ^{12}C beams because of their short and low dose fragmentation tails. The finite range is determined by the initial energy of the ^{1}H or ^{12}C ions and the densities and stopping powers along the beam path. The dose increases slowly with the depth until approximately the terminal ~ 10 mm of the range and then rises very steeply to produce a Bragg peak. The dose decrease deep to the Bragg peak is precipitous. These points are illustrated by plots of depth–dose curves for pristine ^{1}H and ^{12}C beams in Fig. 1.

Use of these beams makes feasible the planning and delivery of biologically effective dose (BED) distributions which are manifestly superior to those by the highest technology x-ray therapy for all but a small fraction of tumors. This means that for a defined dose and dose distribution to the target, there is a lesser dose to uninvolved normal tissues.

For proton and carbon ion beams, the Bragg peak decreases in height with beam energy, i.e. the depth of penetration, as shown in Fig. 2 for pristine ^{12}C ion beams of 135 MeV, 270 MeV and 330 MeV, from Ref. 54. This is due to energy straggling and nuclear interactions; additionally for carbon beams there is fragmentation of the ^{12}C ions, and additionally the peaks broaden with the depth of the peak.

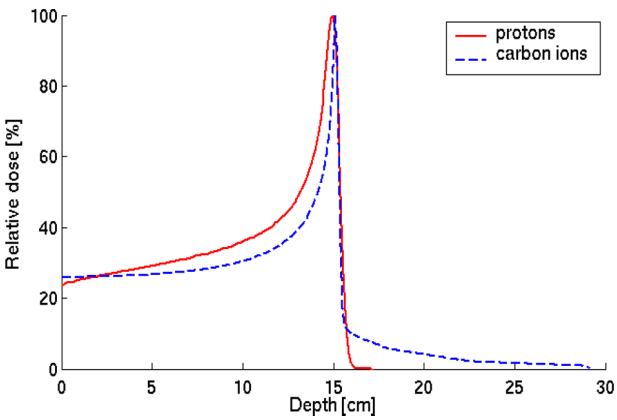

Fig. 1. Depth–dose curves for pristine ^{1}H and ^{12}C beams, demonstrating the very steep Bragg peak and extremely sharp fall in the dose immediately beyond the Bragg peak. On the ^{12}C curve, there is a fragmentation tail. (*Prepared by Trofimov from MGH data and data from GSI, Ref. 31.*)

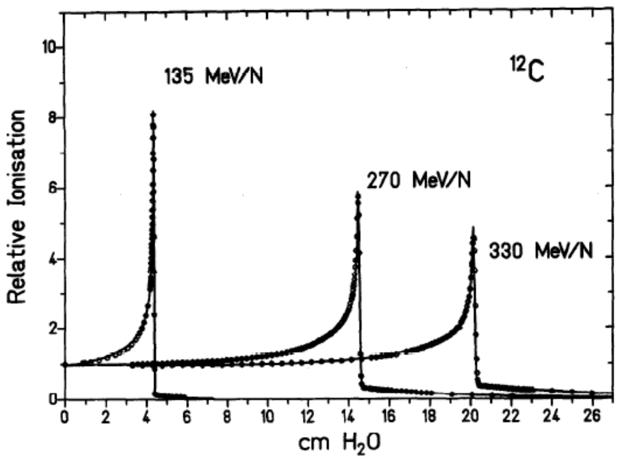

Fig. 2. A plot of dose vs. depth of the Bragg peaks of pristine ^{12}C ion beams of 135 MeV, 270 MeV and 330 MeV [54].

A clinical beam is designed to provide a nearly uniform BED over the range in depth that covers the target from its most proximal to its most distal aspect plus a small margin for errors in positioning the target on the beam and in estimation of the beam range in the patient. This is achieved by the layering of beams of graded energies along the depth of interest so as to generate a flat dose — say, $\pm 5\%$ — in the patient for most anatomic situations, over that length of the beam. This flat region is designated the spread-out Bragg peak (SOBP). This layering of proton beams of selected energies of Bragg peaks was described by Koehler and Preston [30] and is shown in Fig. 3(a). To appreciate the large and clear advantage of a particle beam in radiation therapy, examine the depth–dose curves for a clinical proton beam (with its SOBP) and a high energy x-ray beam, in Fig. 3(b). The x-ray dose is markedly higher distal to the target, due to the fact that it decreases exponentially in the beam path and exits the body. This contrasts with the near-zero dose from a proton beam deep to the target. Additionally, the dose proximal to the target is lower for the ^{1}H beam except for the initial few mm. An important point is that this advantage obtains for each beam path. A similar set of curves could be drawn for ^{12}C ion beams. This difference between the depth–dose curves of particle and x-ray beams is neither subtle nor trivial.

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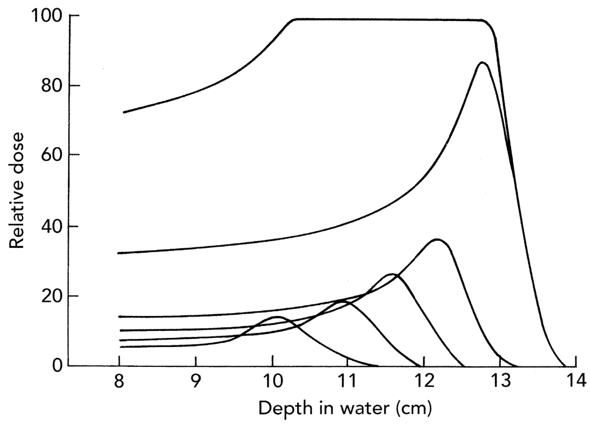
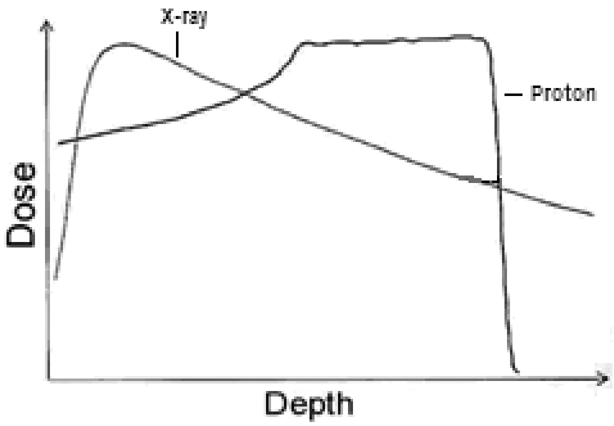


(a)



(b)

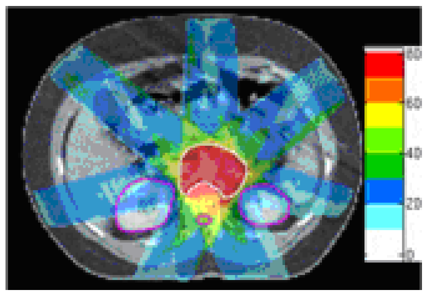
Fig. 3. (a) The SOBP for a ^{1}H beam is produced by layering proton beams of the required energy distribution to achieve a flat (±5%) dose over the depth that includes all of the target plus a thin margin [30]. (b) Depth–dose curves for a representative clinical proton and a high energy x-ray beam.

The biological effectiveness of ^{1}H and x-ray beams is quite similar. Namely, the median RBE determined at clinical dose levels on *in vivo* experimental systems has been estimated to be 1.10. This is based on an analysis of all published data by Paganetti *et al.* [42]. The International Commission on Radiological Units (ICRU) has recommended that the RBE for clinical proton therapy be 1.10 and be used as a generic RBE. That is to say, this one RBE value should be employed for all dose levels, tissues, end points and other parameters. Clinically relevant is the fact that this RBE of 1.10 is less than or equal to the RBE of 1.10–1.15 of 250 kVp x-radiations.

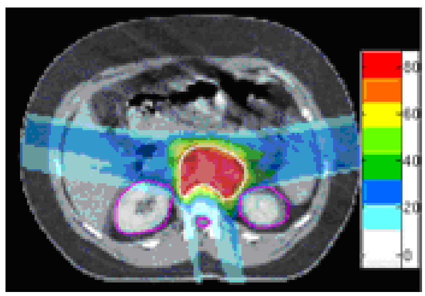
This difference in the dose distribution between x-ray and ^{1}H beams is the one and only rationale for ^{1}H therapy, viz. superior dose distributions of low LET radiations. This dose distribution rationale obtains for ^{12}C as for ^{1}H therapy. Further, ^{12}C beams are high-LET and consequently have a high RBE relative to ^{1}H beams. High-LET–high-RBE radiation provides the prospect of a greater effect on tumors than on normal tissues, *vide infra.*

Further, for high technology x-ray therapy, e.g. intensity-modulated x-ray therapy (IMXT), there are more beams than for particle therapy for nearly all treatment plans. Figure 4 shows an example of the larger number of fields employed for IMXT than for IMPT (intensity-modulated proton therapy). An important aspect of ^{1}H and ^{12}C treatment is the more stringent requirement for accurate positioning due to the steep decline of the dose at the end of the beam's range. That is to say, a small error could result in an almost-zero dose to a small segment of the target and thus a lower tumor control probability (TCP).

The ^{12}C beam fragmentation tail is produced by atomic fragments secondary to ^{12}C ion collisions with atoms in the beam path. These fragments are of moderate-to-low energy and are projected



(a)



(b)

Fig. 4. A treatment plan for irradiation of a prevertebral mass by IMXT and IMPT.

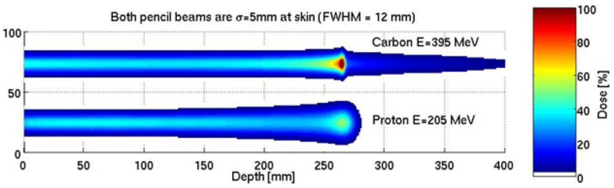


Fig. 5. Ionization along a ^{1}H and a ^{12}C beam and extension of the dose by nuclear fragments generated upstream from the Bragg peak to form the ^{12}C fragmentation tail, but no tail on the ^{1}H beam.

principally in the forward direction. They are predominately protons plus a lower fluence of helium-to-boron nuclei [20]. The physical dose and BED in the tail are low. The fragmentation tail is the one aspect of the BED distribution by ^{12}C beams that is less favorable than that by ^{1}H beams. These fragmentation tails are not judged to constitute an important issue for ^{12}C ion therapy.

Particle beams are generated by cyclotrons, synchrotrons or synchrocyclotrons. The clinically required distribution of energies is achieved by two general techniques. Presently, the most commonly employed ^{1}H beam is designated passive energy modulation (PEM), viz. a broad beam of the required energy transits a rotating range modulator of graded thickness designed to yield the distribution of particle energies that penetrates to the planned depth. Additionally, to generate the energy distribution to provide a uniform dose over the 3D distal contour of the irregularly shaped target, the beam next transits a 3D compensator that defines the particle range over each small segment of the target. For a near-uniform dose distribution transversely across the target, scatterers are employed. To define the lateral borders of the field and reduce the penumbra, i.e. sharpen the beam edge, specially made collimators are prepared for each field in each patient treated by a PEM beam.

There is rapidly increasing interest in the second beam category, viz. pencil beam scanning (PBS). This technique scans a narrow pristine beam over the field of interest with changing particle fluence and energy in order to provide the desired dose distribution throughout the target. Lomax *et al.* [35] wrote of the gains in dose distributions expected from PBS that he and colleagues at the Paul Scherrer Institute have demonstrated. Their results encourage conversion from PEM to PBS for some treatment rooms and for new accelerators to come with PBS capability. Note that the dose distributions over the distal surface of the target are virtually equivalent for the PEM and PBS techniques. The dose conformation around the proximal margin is readily obtained by PBS but not by PEM.

2.2. *Need for gantries*

A central factor in striving for the very best dose distribution in the patient is the use of gantry systems. The patient is in most instances in the supine position, the most comfortable. Further, the patient is not required to move, nor is the tabletop for other than non-coplanar fields. Immobilization procedures are more effective if applied to comfortable patients. Gantry systems are standard features of current x-ray linear electron accelerators. Although gantries for particle beam therapy are large, complex and costly, they are important for achieving the best feasible dose distribution. A gantry system should provide the same flexibility of planning and delivery of the radiation dose as that of conventional x-ray therapy in terms of beam number, beam direction, intensity modulation and 4D IGRT. Thus, to employ particle beams with only a fixed horizontal and/or vertical beam(s) loses some of their dose distribution advantage. Several aspects of the complexities of planning ^{12}C ion therapy have been reviewed by Kramer *et al.* [31, 32].

2.3. *Penumbra*

The penumbra width of ^{1}H beams varies quite widely with the particular design of the beam line, the use of collimators, and the distance between the beam defining mechanism and the patient surface and the depth in tissue being considered. Collimated PEM ^{1}H beams with 4 cm compensators and air gaps of 1, 11 and 21 cm have penumbras [80%–20%] at 10 cm depths of 6, 9.3 and 13 mm. Penumbras at 30 cm are 12, 14 and 17 mm [48]. For comparison, the penumbra for a 6 MV x-ray beam increases from 6.8 to 10.1 mm at depths of 10 and 30 cm. The penumbras are wider for higher energy x-ray beams; for example, the penumbra of an 18 MV x-ray beam at 10 cm is 7.9 mm. With few exceptions, the ^{12}C penumbra is more narrow than for ^{1}H beams, e.g. 1.5–3 mm covering a wide range in depth. This varies only slightly with the various factors mentioned for

^{1}H beams. For further consideration, see Ref. 28. The BED lateral to the penumbra for the PEM proton beam is largely due to low energy neutrons and is similar to or slightly lower than for high energy x-ray beams. The lateral scattered doses for proton beams are low energy neutrons; we have used the neutron BEDs provided by the authors. Also, the lateral dose from carbon beams is less than that from x-ray beams. The papers concerning this lateral dose include Refs. 37, 57, 68, 69 and 71.

2.4. *Heterodensities in the beam path*

A problem in achieving the planned dose distribution for particle beams is the impact of high and low density structures in the beam path, e.g. bone or air cavities. The positions of the margins of structures of differing density in the beam path can be defined in 3D or 4D. Additionally, the density throughout the structure can be determined. With this information, the required beam energy in each voxel can be computed to avoid a shortfall in the range due to, say, bone or an overshoot due to, say, a sinus cavity. To allow for uncertainty in the position of the structure of concern, there will be a narrow rim of the overshoot near the projected margin of the structure of concern. Goitein *et al.* [18] and Urie *et al.* [64] have defined this problem in treatment planning and have developed methods to correct for the perturbations in the dose secondary to objects with density differing from that of soft tissues.

3. Radiation-Biological Considerations

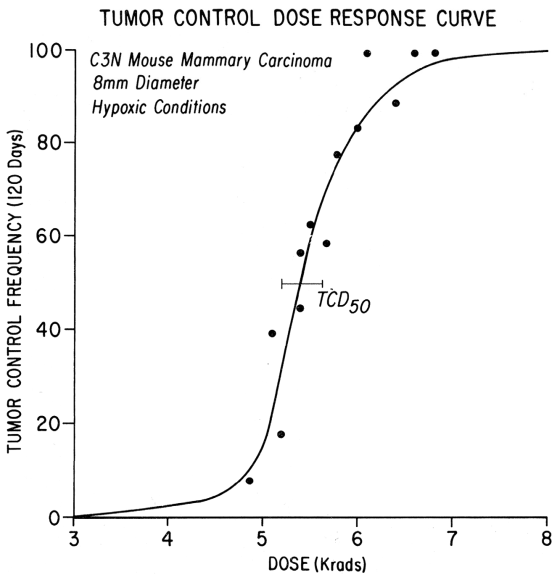
3.1. *Slopes of dose–response curves*

The consequence of a superior dose distribution is an increased tolerance of radiation by the patient, and hence a higher dose can be delivered to the target. This results in a higher TCP with only modest changes in the dose to nontarget tissues due to steep dose gradients between target and normal tissues. Were the TCP judged acceptable but the risk of radiation complications high, the target dose could be unchanged (no alteration in the TCP), but a clinically important decrement in the dose given to the nontarget tissues and accordingly provide a lower NTCP (normal tissue complication probability).

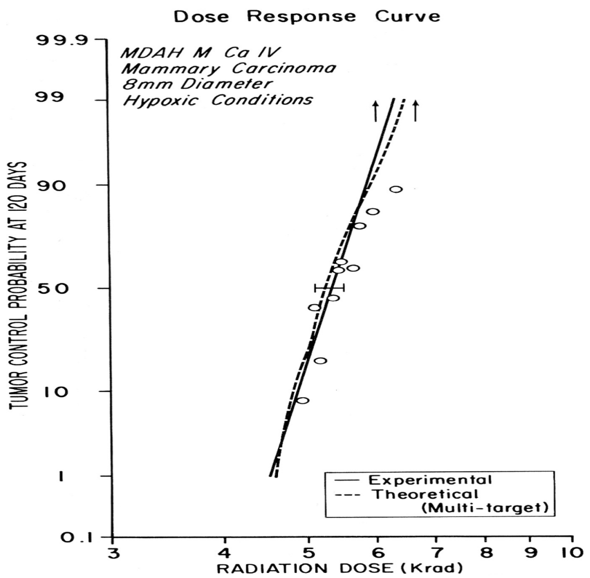
An appropriate question is: What is the likely gain in the TCP from a specific increment of the radiation dose? The answer is that the gain will be a function of the slope of the dose–response curve and the position on that curve of the TCP for the reference treatment. There are, of course, no dose–response curves from studies on human patients. The most secure strategy for considering this question is to examine results from determinations of dose–response curves in laboratory animals. The experiments to consider are those based on spontaneous tumors from inbred animals growing as very early generation transplants in syngenic hosts that are of a narrow age range. The tumor(s) would be transplanted at one time from tumor cells prepared from a small number of tumors of early generation transplants. The resulting tumors would be assigned by a random number process to doses expected to yield TCPs in the range 0.1–0.9. This wide range in planned TCPs increases the accuracy of estimating the slope of the TCP vs. dose curve. The tumors at irradiation should be of a quite narrow range in volume and the radiation distributed uniformly throughout the tumor. Further, the animals need to be monitored for local regrowth for a time that is long relative to the time for regrowth at the highest dose level employed. In the laboratory setting there would be no or only rare subjects "lost to followup." The result is that the dose–response curve would be based on tumors that are virtual clones of a single tumor.

Results from such experiments have been reported and they indicate a steep dose–response curve, viz. γ_{50} of 4.[b] Dose–response curves are S shaped when plotted on a linear–linear grid with the steepest portion in the midrange of $\sim$0.2–0.75, as shown in Fig. 6 [58]. The curve is nearly a straight line if the TCP is plotted on a logit–log dose grid. Thus, were $\gamma = 4$ and the dose increased by 5%, the TCP would be raised by $\sim$20 percentage points. For example, were the TCP of the reference treatment 35% and the dose increased by 5% by a new high technology treatment, the TCP would be raised to $\sim$55%. The maximum steepness of the curve is at a TCP of 37%. It is much more shallow in the TCP ranges of 1–10% and 85–95%.

[b] The γ factor represents the percentage point increase in the response probability for a 1% increase in the dose. γ_{50} is the γ factor at the 50% response point on the dose–response curve.



(a)



(b)

Fig. 6. Dose–response curves for early generation syngenic transplants of a C3H mouse mammary carcinoma irradiated at an 8 mm diameter and under conditions of local tissue hypoxia. The curve in Fig. 6(a) is a linear–linear plot, and in Fig. 6(b) a logit–log dose plot [58].

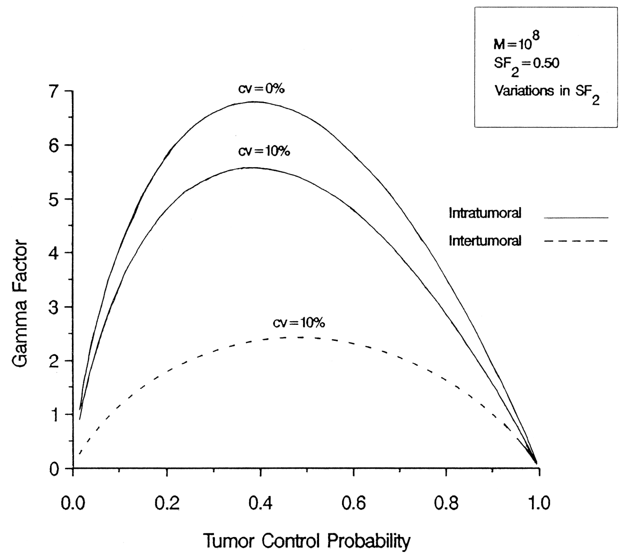


Fig. 7. Curves illustrating the variation of the γ factor for the TCP of a tumor of 10^8 clonogens, and $SF_{0.5}$ is 2 Gy. The three curves are for with zero variation in $SF_{0.5}$, with an intratumoral or an intertumoral 10% coefficient of variation [59].

The slope of the dose–response curve is based on tumors in a heterogenous population that have some level of heterogeneity in tumor characteristics and treatment delivered and that results in a flattening of the curve, depending on the degree of heterogeneity. The impact of population heterogeneity is illustrated in Fig. 7, showing the γ factor vs. tumor control probability for a model tumor system of 10^8 clonogens characterized with a zero or with an intratumoral or an intertumoral coefficient of variation of 10% in SF_2 [59].

The obvious implication is that the examination for a change in the TCP for a specified percentage increase in the dose would be most likely to be successful were the TCP of the reference treatment near the midpoint of the dose–response curve and with the minimum feasible heterogeneity in the tumor/subjects.

3.2. *LET and RBE*

Clinical ^{12}C ion beams are high-LET, viz. up to 120–200 keV/μm extremely close to the end of the range. This adds significant complexity to treatment planning due to the dependence of cell/tissue response on an array of parameters on LET. These are RBE, dose, α/β, the specific cell or tissue, pO_2 and cell age in the cell replication cycle. This complexity is enhanced by the variation of LET over the entire beam path, viz. the entrance to the end of the fragmentation tail, as discussed above.

Clinical practice has essentially employed a generic RBE, as there has not been an adequate database that would make estimation of an integrated RBE feasible for the complex of different tissues in the treatment volume. Fortunately, the generic RBEs employed have proven to be clinically effective, i.e. the frequency of severe radiation injuries has been judged to be acceptable.

RBE increases slowly with LET over most of the range and then rather sharply over the terminal 10 mm of the range, peaking at 100–200 keV/μm.

There is not a uniform RBE–LET relationship, as demonstrated by published RBE vs. ^{12}C LET for difference cell lines. Furasawa *et al.* [16] determined $SF_{0.1}$ of V79, HSG and T1 cell lines for single dose irradiation under aerobic conditions by $\sim$40 and 100 keV/μm ^{12}C ion and 200 kVp x-rays under aerobic conditions. The $RBE_{0.1}$ values for the three cell lines at 40 keV/μm were 2.36, 1.80 and 1.72, respectively. At 80 keV/μm, the $RBE_{0.1}$ values were 3.10, 2.61 and 3.18. Weyrather *et al.* [66] also reported large RBE differences between V79 and CHO cell lines over the LET range 40–80–200 keV/μm. Thus LET, as defined by keV/μm for a specific beam, does not provide a certain guide to the RBE of a different cell line irradiated by the same beam.

The design of a clinical ^{12}C beam requires the adjustment of the physical dose to balance the impact of RBE increasing over the depth to be in the SOBP. This is illustrated in Fig. 8 for a 135 MeV ^{12}C ion beam whose range is 4 cm and planned for a 3 cm SOBP, from Ref. 27. The RBE is that for V79 cells and the end point is $SF_{0.1}$. This is the process employed for the design of most clinical ^{12}C beams.

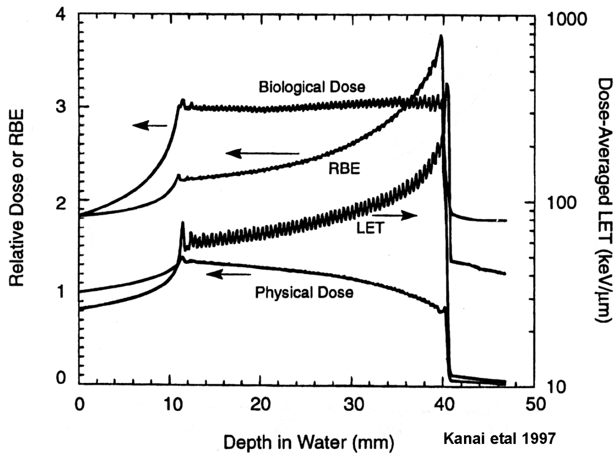


Fig. 8. The basic factors in the design of a clinical ^{12}C ion beam are shown here; namely, the increasing LET and RBE are balanced by a declining physical dose across the SOBP [27].

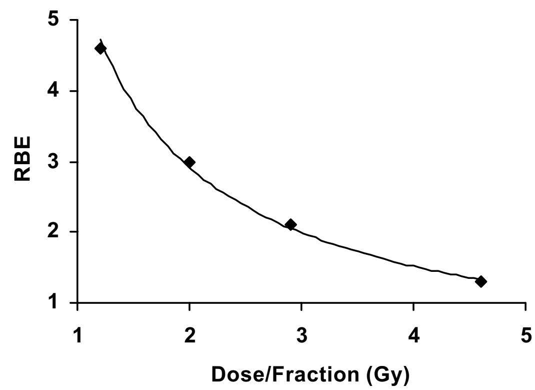


Fig. 9. RBE 42 MeV neutrons vs. x-ray dose per fraction for injury of the pig kidney given in 1–30 fractions [46].

3.3. *RBE and dose*

For high LET beams, there is a clinically very important inverse relationship between RBE and dose. The essential point is that over the clinical dose/fraction range of 1–10 Gy, the RBE increases as the dose is decreased. Figure 9 is a plot of RBE for injury to the normal kidney of female pigs for 42 MeV neutrons and 250 kVp x-rays [46]. The radiation was given as a single dose and in 6, 12 and 30 fractions in 39 days. The RBE moved up from 1.2 for a single dose to 4.6 Gy as the x-ray dose/fractions decreased from 7.9 to 1.4 Gy. This is a big effect and merits careful consideration in treatment planning.

3.4. *OER*

There has been serious and sustained interest in high LET radiation for some five decades, principally due to three facts: (1) many epithelial and mesenchymal tumors have hypoxic foci; (2) OER[c] is $\sim$2.5–3 for x-radiation; and (3) OER is lower for high LET radiations. Thus, the RBE would be higher for cells that are hypoxic than for similar cells that are normally oxygenated. Accordingly, the effect of high LET irradiation of tumors containing hypoxic cells would be greater than that of low LET irradiation. The prediction would accordingly be an increased TCP with

[c]OER is the ratio of the dose to inactivate a cell under hypoxic conditions to that under aerobic conditions.

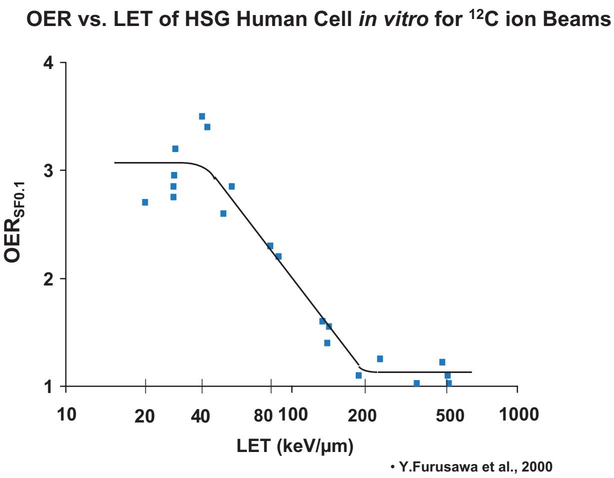


Fig. 10. OER vs. LET for the HSG cell line [16].

no increased NTCP for high LET irradiation of such tumors.

OER varies widely over a rather narrow range of LET, as shown in Fig. 10. This is a plot of OER vs. LET for a human salivary gland tumor cell line and is drawn from Ref. 16. The OER is relatively constant with rising LET up to about $\sim 40\,\mathrm{keV}/\mu\mathrm{m}$. Then, as LET increases from ~ 50 to 200, OER falls to ~ 1.1. For ^{12}C ion therapy requiring SOBPs of 6–12 cm, OER at the mid-SOBP is likely to be $\geq \sim 2.2$. Thus, for most of the SOBP, OER would be expected to be 2–2.5, a relatively modest but certainly not negligible change in the desired direction.

An early finding of cellular radiation biology was a variation of radiation sensitivity with position in the cell replication cycle, i.e. the age response function. The magnitude of this variation is cell-line-dependent. The late S phase is generally the most resistant and the M phase the most sensitive phase. There is a flattening of the age response function with increasing LET, and at very high LET it is almost flat. (See Ref. 45.) This is a factor for tissues with a high proportion of cells actively dividing, viz. acute responding normal tissues and some tumors. In contrast, this would be a small factor in the response of late responding tissues.

4. Clinical Outcome Data

We consider the local control and treatment–related morbidity results from reports on seven groups of tumors: chordoma and chondrosarcoma of the skull base and upper cervical spine, uveal melanoma, head and neck carcinoma (squamous cell and adenocystic), non-small-cell lung carcinoma (NSCLC), hepatocellular carcinoma (HCC) and prostate carcinoma. For several of the series, results are given for an approximate median of doses applied. Regarding the stage of disease, for some reports the statement is that the patients had locally advanced tumors. The column headed "Serious radiation injury" gives the data for $\geq$ GII or $\geq$ GIII complications, or for some series the injuries are listed as serious.

Note that ^{12}C radiation has been deployed as hypofractionated therapy and ^{1}H predominately as "standard fractionation," viz. doses of 1.8–2 Gy (RBE).

4.1. *Chordoma*

A large number of patients have been treated by ^{1}H and ^{12}C beams for chordoma of the skull base and upper cervical and spine, especially considering their rarity. The data in Table 1 give 5-year ^{12}C local control rates of 91% and 100% by 60 Gy (RBE) for doses/fractions of 3–3.8 Gy (RBE), compared with

Table 1. Chordoma of the skull base and upper cervical spine.

Beam	Number of patients	Dose Gy (RBE)		Local control at years	Late injury at years	Reference
		Total	Per Fx			
^{1}H	115	69	1.8	59% at 5	Not given	[60]
	42	74	1.8–2	81% at 5	High grade 6% at 5	[1]
^{12}C	19	61	3–3.8	91% at 5	None	[21]
	10	(48–58)		60% at 5		[21]
	12	> 61–790	3.0–3.5	100% at 5	2 patients	[52]
	84	≤ 60		63% at 5		
x	37	67	1.8	50% at 5	Serious in 1 (3%)	[7]

54% and 81% for ^{1}H doses of 69 Gy and 74 Gy (RBE) at conventional doses per fraction. Importantly, the TCP values are higher and apparently the NTCP a bit lower for ^{12}C than for ^{1}H-treated patients.

Results are available from ^{1}H and ^{12}C irradiation of sacral chordoma. Imai *et al.* [25] treated 30 patients for chordoma of the sacrum by ^{12}C ion beams to 70.4 Gy (RBE) in 16 fractions and no surgery. They have had 95% local control of tumor in the defined PTV. That is to say, there has been one in-field failure and that was of a 1470 ml lesion. There were, however, 6 failures in relatively nearby tissues, e.g. gluteus, coccyx, spinal muscle, buttock femoral muscle (2 patients) and lumbar spine. These results suggest that some of these might well have represented wider subclinical extensions of disease than appreciated at the start of treatment. Park *et al.* [43] have reported on 21 patients treated by ^{1}H + x-radiation and surgical resection for sacral chordoma. The local control results were 12/14 and 1/7 for primary and locally recurrent (after prior surgery). In the ^{12}C series 2 patients required skin grafts but no other serious persisting treatment-related morbidity. Six patients had temporary neurological symptoms. In 12 patients with a primary tumor of the ^{1}H + surgery series there were 4 colostomies and 2 with incontinence; whether these adverse events were principally the result of the radiation or surgery cannot be definitely stated.

4.2. *Chondrosarcoma*

Results from ^{1}H treatment were markedly better for chondrosarcoma than for chordoma of the skull base, viz. 5-year local control rates, 94–98% vs. 54–81%. ^{1}H therapy has a modest numerical gain relative to ^{12}C therapy, Table 2.

Table 2. Chondrosarcoma of the skull base and upper cervical spine.

Beam	Number of patients	Dose Gy (RBE)		Local control at years	Reference
		Total	Per Fx		
^{1}H ± x*	200	72	1.8–2	98% at 5	[47]
	22	68	1.8–2	94% at 5	[1]
^{12}C	54	60	3	90% at 4	[49]

*Surgery was gross total removal in 5% of patients.

4.3. *Uveal melanoma*

A group of tumors for which several radiation methods have provided quite high local control rates is uveal melanoma as documented in Table 3. The TCP values have been > 95% and the NTCP (enucleation) rate 6–7% for treatment with ^{1}H and ^{12}C [9, 11, 12, 19]. These treatments have been quite-high-dose, viz. 60 Gy (RBE) in 4 fractions or 70 Gy (RBE) in 5 fractions. The dose of 70 Gy (RBE) in 5 fractions would be estimated to be the BED equivalent of 280 Gy at 2 Gy/fraction for $\alpha/\beta = 2$ and 140 Gy for $\alpha/\beta = 10$. For 60 Gy (RBE) in 4 fractions, the BED equivalents would be 255 Gy and 125 Gy. The yield for SRT at 2.8 years in a series of 158 patients was 98%, but with the enucleation rate of 13% [10]. With really large numbers of patients, and very high local control and eye preservation rates at 10 and 15, ^{1}H therapy appears, at present, to be the most effective radiation treatment for uveal melanoma.

4.4. *Head and neck*

Here, the results of irradiation of squamous cell carcinoma (nonskin) appear to give a definite advantage to ^{1}H therapy over ^{12}C therapy, Table 4. This is based on the reported 5-year local control rates of 56% for ^{12}C vs. ∼93% for ^{1}H therapy [39, 56]. Note that these results from ^{12}C therapy are based on small patient numbers. Even allowing for the small patient numbers, these results do not support the expectation that ^{12}C radiation is especially effective against tumors, with head/neck carcinomas even though characterized as having a high probability of hypoxic foci.

The reported results of particle beam irradiation of locally advanced adenocystic carcinomas indicate a higher local control rate for ^{1}H + x than for ^{12}C therapy, viz. 93% vs. 78–79% [39, 44, 51]. However, these ^{1}H results have been associated with a quite high incidence of serious radiation injury, i.e. developing in 16 of the 23 patients. This has been discussed with Dr. A. Chan, an MGH (personal communication, 2009) head/neck radiation oncologist, who states that in patients treated after 2002 the treatment has been 1.8 Gy (RBE) once daily (no BID), substantially smaller CTVs, dose levels of ∼70 Gy (RBE) (protons only) and combined with chemotherapy. The frequency of radiation injury is now much lower. Of note is the report by Schulz-Ertner of local

Table 3. Uveal melanoma.

Beam	Number of patients	Dose Gy (RBE)		Local control at years	Enucleation	Reference
		Total	Per Fx			
^{1}H	2069	70	14	95% at 15	7%	[19]
	2435	60	15	95% at 10	~7%	[11, 12]
	1406	60	15	96% at 5	8%	[9]
^{12}C	57	70 (60–85)	~14	97% at 3	5%	[62]
x	132	60	12	98% at 2.8	13%	[10]
	25	70	14			

Table 4. Head and neck.

Beam	Number of patients	Dose Gy (RBE)		Stage	Local control at years	Injury GIII	Reference
		Total	Per Fx				
Squamous cell carcinoma							
^{1}H ± x	29	76	~1.7	T1–T2 13	12/13	3 patients	[56]
				T3 10	9/10		
				T4 6	6/6		
^{1}C	15	57.6–64	3.6–4	Advanced	56 % at 5	None	[39]
Adenocystic carcinoma							
^{1}H + x	23	76	1.8 1.6 BID	Gross tumor at RT in 20	93% at 5	16 patients*	[44]
^{12}C	90	58–64	3.6–4	Advanced	79%	None	[39]
^{12}C + x	29	72	1.8 x 3 × 6 ^{12}C	Advanced	78% at 4	1 patient	[51]
x	34	66	1.8		25% at 4	2 patients	

*1 GIV retinopathy, 3 required surgery, 10 CNS (7 seizure, 3 short term memory), 2 other.

control rates of 78% by 72 Gy (RBE) vs. 25% by 66 Gy [51], i.e. dose is important. These data are not from a random assignment of patients to one of the two dose levels. Recognition must be given to the lack of knowledge in any detail of the extent of tumors in these diverse series and, hence, interpretation of the data can only be tentative.

4.5. *Non-small-cell lung carcinoma*

A substantial number of patients have been treated by ^{1}H or ^{12}C beams for their early stage NSCLC, Table 5. Studies on both beams employed hypofactionation, i.e. 10 or 12 fractions [4, 22, 38]. Higher success rates were obtained by ^{12}C therapy for stages T1 and T2, viz. 95% at 5 years for ^{12}C ions using 8 fractions to 72 Gy (RBE). The ^{1}H results were 87% and 49% for T1 and T2 tumors at lower BED dose levels. Related morbidity in particle beam therapy has been low, at least up to this time. The extremely aggressive x-ray treatment by Fakiris *et al.* of 60–66 Gy in 3 fractions obtained local control of 88% at 3 years. Note that the BED for 60 Gy in 3 fractions would be 330 Gy at 2 Gy/fraction for $\alpha/\beta = 2$ and 150 Gy for $\alpha/\beta = 10$ [13]. The serious injury rate was 10% for peripherally sited lesions but 27% for central lesions. Notably, five of their patients had a Grade V radiation injury Forquer *et al.* [14]. have reported a nonnegligible frequency of brachial plexopathy following hypofractionated x-irradiation of the apical region of the thorax.

4.6. *Hepatocellular carcinoma*

Primary liver cancer is one of the most frequent carcinomas in humans and is a disease for which the role of radiation has traditionally been limited to palliation. However, results from ^{1}H and ^{12}C therapy have

Table 5. Non-small-cell lung carcinoma.

Beam	Number of patients	Dose Gy (RBE)		Stage	Local control at years	Serious or ≥ Glll	Reference
		Total	Per Fx				
^{1}H	68	51–60	5.1–6	T1 + T2 T1 T2	74% at 3 87% 49%	None	[4]
	21	55* or 66	5.5 or 6.6	T1 A + B	95% at 2	None	[22]
^{12}C	51	72	8	1	95% at 5	1 (skin)	[38]
x	70	60 66	20 22	T1 + T2	88% at 3	≥ GIII Peripheral 10% Central 27%	[13]

*Dose was specified in Gy in their paper. These have been converted to Gy (RBE) by multiplying by 1.1.

Table 6. Hepatocellular carcinoma.

Beam	Number of patients	Dose Gy (RBE)		Stage	Local control at years	Serious or Injury ≥ Glll	Reference
		Total	Per Fx				
^{1}H	51	66	6.6	Child–Pugh A (80%) B (20%)	88% at 5	8 of 41 Child–Pugh A → B None to C	[15]
	162	72 (median)	∼4.5	60% stage II–IIIB	87% at 5	5 with ≥ GII	[5]
^{12}C	24 86	∼64.5 ∼62–50	4.2 ∼5.2–12.6	Not given	81% at 5 87% at 5	Child–Pugh ↑ ≥ 2 points in 18%	[29]
	47	52.8	13.2		96% at 5	No serious skin, GI injuries	

to be rated as impressive. For two ^{1}H therapy studies at Tsukuba, the 5-year local control results have been 87–88% [5, 15]. High grade treatment–related morbidity has been of low frequency. The more recent ^{12}C dose escalations study by Kato *et al.* [29] from Chiba has yielded progressive gains in the TCP as the dose/fraction was increased from ∼49.5 to 79.5 in 15 fractions [3.6 Gy (RBE)/fraction] to 52.8 Gy (RBE) in 4 fractions [13.2 Gy (RBE)]. Namely, the TCP rose from 81% to 96% (47 patients) at this very high dose.

4.7. *Prostate carcinoma*

Among US men, this is a quite common tumor and the proportion diagnosed in an early stage is high. The local control and bNED rates for early stages of tumors by high dose radiation are high. This is achieved at a low frequency of serious radiation-related morbidity. For ^{1}H + x radiation treatment of stage T1c–T2c prostate cancer treated by 74 Gy at 2 Gy (RBE)/fraction, the 5-year bNED result was 74% [55]. The critical role of doses is evident by the 5-year bNED rates of 61% and 80% following 70.2 vs 79.2 Gy (BRE) to stages 1b–2b prostate cancers in a Phase III clinical trial [73]. A higher success rate has been reported by Tsujii *et al.* [62] for ^{12}C ion treatment, viz. 5-year bNED rate of 92% and with no serious complications for 295 patients with stage T1 and T2 disease given 66 Gy (RBE) at 3.3 Gy (RBE)/fraction. Note that for IMXT treatment to 81 Gy by Zelefsky *et al.* [72], the 8-year bNED rate for 425 and 101 patients classed as ASTRO risk groups, low and intermediate stage, were 85% and 76%, respectively, Table 7.

The first study of ^{1}H beam treatment of prostate patients was done by Shipley *et al.* [53] for T3–T4 tumors, through a phase III trial with treatment by x-ray alone to 67.2 Gy or 50.4 Gy + a 25.2 Gy (RBE) ^{1}H boost; the total dose was 75.6 Gy (RBE). Local

Table 7. Prostate carcinoma.

Beam	Number of patients	Dose Gy (RBE)		Stage	Local control at years	≥ Glll injury	Reference
		Total	Per Fx				
x + ^{1}H			1.8x → 50.4	T3–T4			[54]
vs.	93	75.6	2.1 ^{1}H		77% at 8	R[a] 9% vs. 2%	
x + x	96	67.2	2.1 x		60% at 8	U 4% vs. 2%	
x + ^{1}H	1255	74	2	T1c–T2c	bNED 74% at 5	GIII 2%	[56]
x + ^{1}H	197	50.4 x 28.8 ^{1}H	1.8	T1b–T2b	bNED 80% at 5	1% 1%	[74]
	96	50.4 x 19.8 ^{1}H	1.8		bNED 61% at 5	2%	
^{12}C					bNED	None	[63]
	295	66	3.3	T1–T2	92% at 5		
	162			T3	81% at 5		
x	561	81	1.8	Risk (ASTRO)	bNED at 8 85%	3%	[73]
	425			Low	76%		
	101			Medium	72%		
	35			High			

[a]R is late rectal bleeding. U is late urethral stricture.

control at 8 years was reported as 77% and 60% for the high and low dose groups.

5. Discussion

Proton and carbon ion beams provide clearly superior dose distributions for most sites relative to that achievable by the highest technology x-ray beam therapy, due to the physical fact that the particle beams have finite ranges. This results in the advantage of near-zero doses deep to the target for each beam path. This distal dose can be contoured to match closely the deep margins of the target plus the PTV. Further, for PBS dose delivery the high dose zone can be contoured to the proximal margins. For gantry-equipped treatment rooms, these particle beams have the same flexibility in dose delivery as modern x-ray machines, viz. beam number, direction, intensity modulation and 4D IGRT. ^{12}C beams have one physical advantage over ^{1}H beam, and that is a narrower penumbra, except for penetration depths of only a few cm. The narrower penumbra is judged to be clinically significant in radical dose therapy where important late responding normal tissues are in close proximity to the target. The late responding tissues tend to be low α/b and hence at increased risk of radiation injury by high LET beams, e.g. ^{12}C. Thus, the slimmer penumbra of ^{12}C beams, i.e. 1.5–3 mm compared with the much wider penumbras of ^{1}H beams, is rated as an advantage. This is so as the tissues included in the penumbra would be normal tissues, and in many instances late responding tissues.

The attraction of high LET beams for radiation therapy has been focused on a reduced OER. The OER is reduced from ∼3 to 2–2.5 at the mid-SOBP, i.e. a modest but nonzero reduction. The data from a good number of clinical studies of the efficacy of fast neutron (high LET) and x-ray therapy for head/neck carcinomas have not yielded outcome data favoring neutron therapy. These data are in part from clinical trials with comparable depth–dose characteristics for the neutron and x-ray beams. The general finding has been excessive rates of serious injury to normal tissues with no important gain in TCP. The relevant studies include those by Cohen [6], Hussey *et al.* [23, 24] and Maor *et al.* [36]. Head/neck squamous cell carcinomas were heavily represented in several of these studies. Multiple studies on untreated squamous cell carcinoma of the head/neck have demonstrated hypoxic regions. These studies include those by Becker *et al.* [2]; Brizel *et al.* [3] and Nordsmark *et al.* [41]. There is one apparently quite bright outcome for neutron therapy, and that is for treatment of salivary gland carcinomas. The local controls result is higher for neutrons than for x-rays in a prospective trial [33]. However, that result is perhaps not related to the reduced OER of neutrons. Wijffels *et al.* [67] examined in considerable detail a series of salivary gland carcinomas for evidence of hypoxic cells and found none. The overall experience in neutron therapy has been a setback for high LET radiation therapy. This shift in attitude is reflected by the fact that in the US there were eight centers and five have now closed. The status of neutron therapy has been reviewed by Laramore *et al.* [34], who judged that there was ample basis for continued study of neutron therapy for salivary gland tumors. They also suggested that further study be directed to sarcomas of soft tissue and bone, as well as selected carcinomas of the lung.

Consider the substantial difference in local control of squamous cell carcinomas by ^{1}H and ^{12}C ion therapy given in Table 4, viz. $\sim 90\%$ for ^{1}H and 56% for ^{12}C. Despite the small numbers, these results do constitute a disappointment.

The results obtained by ^{12}C ion therapy for chordoma of the skull base and sacrum are definitely impressive. The high local control rate associated with no serious complication rate (at least till 2008) appears to constitute a clinical gain. The ^{12}C dose was evidently highly successful in the inactivation of chordoma in the designated PTV. The frequency of local regrowths in the adjacent tissues raises concern regarding our ability to estimate the extent of subclinical disease.

Also, the success of stage 1 NSCLC appears positive. However, the results from ^{1}H irradiation are, at present, at least as good as that from ^{12}C therapy for chondrosarcoma of the skull base, uveal melanoma, squamous cell carcinoma of the head/neck, hepatocellular carcinoma, and also prostate cancer. The very high success rates in the irradiation of two additional tumors could also be classed as noteworthy. One is a small series of 10 patients treated by ^{12}C ions for their primary renal cell carcinoma [40], and obtained a 5-year local control rate of 100%. The second is the 5-year local control of 84% in a series of 72 patients treated by Yanagi *et al.* [70] for mucosal melanoma to ~ 58 Gy (RBE) [~ 3.6 Gy (RBE)/fraction] by ^{12}C ions.

In summary, the clinical data presented constitute a manifest need for phase III clinical trials of ^{1}H vs. ^{12}C therapy. High LET is the one characteristic that clearly distinguishes ^{12}C from ^{1}H beams. The trial should be a prospective randomized study designed to determine if high LET radiation provides a clinical advantage for one or more types of cancer. To achieve this, the design should have identical dose fractionation for the ^{1}H and ^{12}C arms. In addition, there should be fully comparable technology for defining the margins of the target and the alignment of the target on the beam. Further, any combined modality therapy must be the same for the two arms. The protocol should include plans for long term followup examinations. This is critical, as the question is: is there a gain in the TCP for a specified NTCP?

Special effort should be directed toward selecting some tumors for the trials whose TCPs by protons therapy are in the range of 0.2–0.75, i.e. the steepest portion of the dose–response curve. This provides a higher probability of detecting a difference in the TCP of 10% points. In accord with this concern, efforts should be made to have a highly homogeneous group of patients and of tumors.

The rationale for high LET radiation therapy is the expectation of greater efficacy against the gross tumor and no expected clinical benefit for irradiation of grossly normal tissues. Based on this, our opinion that the most effective strategy would be to employ low LET ^{1}H beams for the dose to the CTV (GTV + normal tissues judged to be infiltrated by a subclinical tumor) and then high LET ^{12}C for the boost dose to the GTV. As the object of the trial would be to examine for a positive impact of the highest feasible LET and RBE by ^{12}C therapy, the boost dose should be administered at a low dose/fraction, e.g. ~ 2–2.5 Gy (RBE). As noted earlier, the RBE increases steeply as the dose/fraction is reduced to 2 and 1 Gy (RBE). This high LET boost dose could be given as a concomitant boost, a BID schedule. As the point is to examine for gain by high LET and RBE, the trial should use ^{12}C in the highest feasible RBE mode.

Efforts to assess the cost of particle beam therapy need to consider it as one component of the total societal cost of managing cancer patients. They include screening, diagnosis, patient evaluation, combined modality therapies (chemical, biological and genetic strategies) and the cost of failure, in terms of either recurrence of the tumor or treatment-related morbidity. These are in addition to the actual cost of administering particle beam treatment.

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Herman Suit is a member of the faculty of the MGH and of Harvard Medical School. He has been active in the start of clinical proton radiation therapy in 1973 and that interest has continued unabated.

Thomas F. Delaney is the Director of the Francis H. Burr Proton Therapy Center of the MGH. He is a specialist in tumors of the connective tissues and bones. He is a member of the faculty of the MGH and of Harvard Medical School.

Alexi Trofimov is a clinical physicist in the proton program with special interest in complexities of rt planning and biomathematical modeling. He is a member of the faculty of the MGH and of Harvard Medical School.