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Review

Proton *vs* carbon ion beams in the definitive radiation treatment of cancer patients

Herman Suit [a,*], Thomas DeLaney [a], Saveli Goldberg [a], Harald Paganetti [a], Ben Clasie [a], Leo Gerweck [a], Andrzej Niemierko [a], Eric Hall [b], Jacob Flanz [a], Josh Hallman [a], Alexei Trofimov [a]

[a] *Department of Radiation Oncology, Boston, MA, USA;* [b] *Center for Radiological Research, Columbia University, New York, NY, USA*

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ABSTRACT

Background and purpose: Relative to X-ray beams, proton [^{1}H] and carbon ion [^{12}C] beams provide superior distributions due primarily to their finite range. The principal differences are LET, low for ^{1}H and high for ^{12}C, and a narrower penumbra of ^{12}C beams. Were ^{12}C to yield a higher TCP for a defined NTCP than ^{1}H therapy, would LET, fractionation or penumbra width be the basis?
Methods: Critical factors of physics, radiation biology of ^{1}H and ^{12}C ion beams, neutron therapy and selected reports of TCP and NTCP from ^{1}H and ^{12}C irradiation of nine tumor categories are reviewed.
Results: Outcome results are based on low dose per fraction ^{1}H and high dose per fraction ^{12}C therapy. Assessment of the role of LET and dose distribution *vs* dose fractionation is not now feasible. Available data indicate that TCP increases with BED with ^{1}H and ^{12}C TCPs overlaps. Frequencies of GIII NTCPs were higher after ^{1}H than ^{12}C treatment.
Conclusions: Assessment of the efficacy of ^{1}H *vs* ^{12}C therapy is not feasible, principally due to the dose fractionation differences. Further, there is no accepted policy for defining the CTV–GTV margin nor definition of TCP. Overlaps of ^{1}H and ^{12}C ion TCPs at defined BED ranges indicate that TCPs are determined in large measure by dose, BED. Late GIII NTCP was higher in ^{1}H than ^{12}C patients, indicating LET as a significant factor. We recommend trials of ^{1}H *vs* ^{12}C with one variable, *i.e.* LET. The resultant TCP *vs* NTCP relationship will indicate which beam yields higher TCP for a specified NTCP at a defined dose fractionation.
 Radiotherapy and Oncology 95 (2010) 3–22

Rationale for clinical trials of proton *vs* carbon ion radiation therapy

Clinical proton [^{1}H] and carbon ion [^{12}C] beams provide distributions of dose in Gy(RBE) (in the following text, the term dose for ^{1}H and ^{12}C ion irradiation refers to dose in Gy(RBE)) that are superior to those achievable by the highest technology photon beams due to the finite range of clinical particle beams. This superiority is similar for ^{1}H and ^{12}C ion beams. Two significant dose distributional differences between these two beams are that ^{12}C ion beams have more narrow penumbras (this is correct for nearly all treatment set-ups) and have fragmentation tails. There is a highly important additional difference between the two beams, *i.e.* ^{1}H beams are low LET and ^{12}C ion beams are high LET. A clear and present need is the conduct of clinical trials of ^{1}H *vs* ^{12}C ion beams with a single variable, LET. This requires that the participating ^{12}C ion therapy centers employ a common model for selecting RBE[s] *i.e.* standard descriptions of dose. A critical point in the trial design is that dose fractionation be identical in the two arms. A superior dose distribution is one that for a specified dose and dose distribution to the target delivers a lesser dose to normal tissues adjacent to and distant from the CTV. The effect is to make a higher dose to the target feasible and accordingly yield a higher tumor control probability [TCP] for a near constant normal tissue complication probability [NTCP]. An alternate strategy is to accept the standard TCP and the reduced dose to normal tissues for a lower NTCP. The potential gain from the high LET and high RBE characteristics of ^{12}C ion irradiation may be due principally to a lower oxygen enhancement ratio [OER] and perhaps a smaller variation in radiation sensitivity with position of the cells in the cell replication cycle. Additionally, there would be predicted a higher RBE for slowly growing and low α/β tumors. The late responding tissues are also low α/β and relatively high RBE. In contrast, the α/β of the commonly treated and relatively fast growing tumors would be high and the RBE lower. Accordingly, the results of high LET irradiation would be expected to be better for the low α/β tumors. The late responding tissues are assumed to be similar when surrounding low or high α/β tumors.

The potential of important clinical gains by ^{1}H and ^{12}C radiation therapy has attracted substantial and increasing interest as reflected in the number of patients treated and the number of currently active centers. As of February 2009, the numbers of ^{1}H and ^{12}C treated patients were 61,122 and 5342, and there were 26 and 2 active proton and carbon ion treatment centers in Japan, [Martin Jermann (Martin Jermann is the Secretary of Proton therapy Co-operative Oncology Group), personal communication,

* Corresponding author. Address: Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA.
E-mail address: hsuit@partners.org (H. Suit).

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2009]. In November 2009, the ^{12}C ion and ^{1}H center at Heidelberg opened [J. Debus, personal communication, 2009] as the ^{12}C ion program at the Gesellschaft für Schwerionenforschung [GSI] at Darmstadt was transferred to Heidelberg. Thus there are three carbon therapy centers, Chiba, Hyogo and Heidelberg. A considerable number of both ^{1}H and ^{12}C ion therapy centers are under construction and many more in the planning stage.

There have been several considerations of the merits of particle beams in radiation therapy. These include reviews by Delaney and Kooy [1], Goitein [2], Jones [3], Schulz-Ertner et al. [4] Turesson et al. [5], Weber and Kraft [6] and Brada et al. [7].

Physical basis for superior dose distribution by ^{1}H and ^{12}C ion beams

The superiority of dose distributions by ^{1}H and ^{12}C ion beams relative to X-ray beams is based on the fact of physics that their range in tissues is finite. The depths of penetration are a function of the initial energy of the beams and the density and atomic composition of the tissues along the particle path. Over the distal cm of the end of range, the dose increase is extremely steep resulting in a very narrow and high peak, the Bragg peak (for a brief history of the initial observation and description of the Bragg peak see Brown and Suit [9]). Fig. 1a, from Wilkens and Oelfke [8], presents the relative dose *vs* depth for proton and carbon ion beams. A notable difference between the two beams is the fragmentation tail of ^{12}C ion beams, discussed below.

The relative height of the Bragg peak for ^{1}H and ^{12}C ion beams, with respect to the entry dose, decreases with the beam energy [penetration] due to energy straggling and nuclear interactions leading to fragmentation of ^{12}C ions [10]. There is also an increase in width of the Bragg peaks with beam energy. These changes in the peaks are illustrated for protons in Fig. 1b The peak to plateau ratios for ^{1}H and ^{12}C ion beams vary and are dependent on dose, and hence RBE in the plateau, and the technical details of the design of the beam line. For many plans the ratio is higher for ^{12}C ion beams and in some the ratio favors ^{1}H beams [8].

LET increases with depth on a curve similar to that of dose and this obtains for ^{1}H and ^{12}C beams. The upswing in LET occurs at a slightly greater depth than dose and continues slightly beyond the dose peak, as presented for a ^{1}H beam in Fig. 2. This results in an increased dose on the declining edge of the peak and a very short extension of penetration of the biologically effective dose.

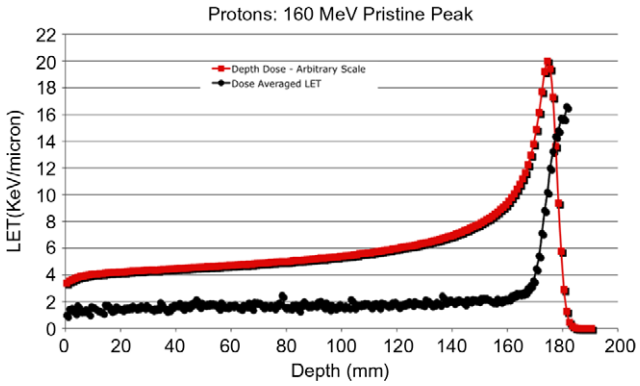

Fig. 2. Increase in dose and LET with depth for a 160 MeV proton beam.

Production of particle beams

Clinical ^{1}H and ^{12}C ion beams are spread out to conform to the target by three general techniques: passively scattered, pencil beam scanning and wobbling or uniform scanning. Presently, the most commonly employed method is passive scattering (including single and double scattering). The beam first passes through a rotating range modulator of varying thickness or a ridge filter to produce a spread-out Bragg peak (SOBP) of the width required to irradiate the target uniformly in depth; this also spreads the beam laterally and an additional scatterer is used to produce approximately uniform fluence across a broad area. The close lateral conformation to the target is achieved with field collimators. To achieve the desired dose contour around the distal margins of the target, the passively scattered (and modulated in energy) beam then passes through a carefully sculpted compensator to realize the planned penetration of the proton or carbon ions in tissue.

Pencil beam scanning [PBS] utilizes an unscattered beam of an appropriate size for the desired penumbra, that is scanned over the field, with the particle fluence and energy actively varied as appropriate, in order to yield the intended dose distribution. The distribution of dose over the distal surface of the defined target is approximately equivalent for passively scattered and PBS beams. However, PBS technology yields a closer conformation to the proximal target surface. Intensity modulated radiation therapy is feasible for ^{1}H and ^{12}C ion beams that are actively scanned. This can also be performed by passively scattered beams but is more difficult.

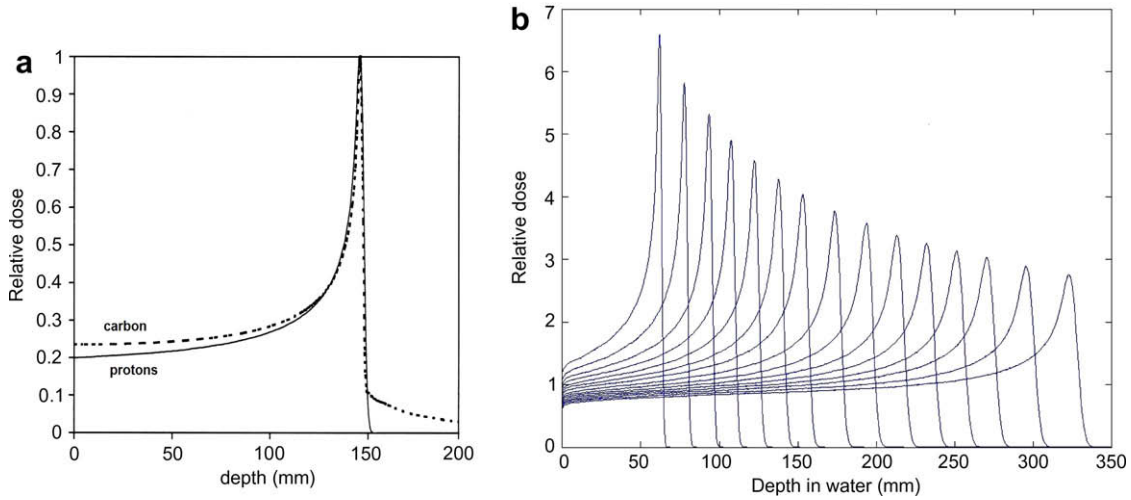

Fig. 1. (a) Relative dose *vs* depth of a proton and a carbon ion beam, with a range of ~14 cm [8]. (b) The decreasing height and increasing width of proton Bragg peaks [normalized by the primary beam fluence] with depth of penetration, personal communication, H. Kooy, 2009.

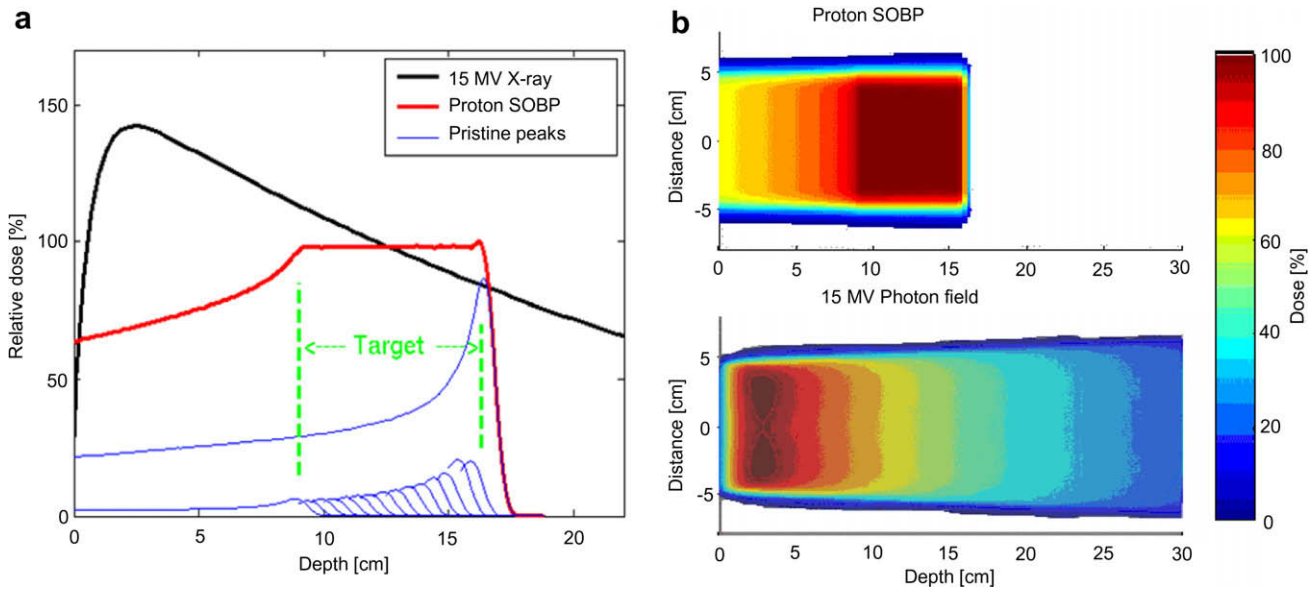

Fig. 3. (a) The layering of selected proton Bragg peaks to achieve an approximately uniform dose over the depth of interest, *i.e.* a SOBP. This is the central axis depth dose for a 150 MeV proton beam with a 7 cm SOBP. For comparison, the central axis depth dose curve of a 15 MV X-ray beam is included. (b) Cross section of dose *vs* depth for a 150 MeV proton beam with a 7 cm SOBP and for a 15 MV X-ray beam is shown.

Wobbling, or uniform scanning, is another delivery option for particle therapy, in which beams are initially spread by a single scatterer and then scanned magnetically along predetermined trajectories, without beam current modulation. Uniform scanning facilitates irradiation of larger fields, compared to double scattering for the same energy incident beam. PBS can accomplish the same goal with an appropriately controlled beam of similar size as the scattered wobbling beam.

SOBP

To design a clinical passively scattered ^{1}H beam, an array of monoenergetic proton beams of graded energies is layered so as to achieve a near uniform dose in Gy(RBE) across the volume of interest or target. This near uniform dose region [±1% (this degree of uniformity pertains to dose in a water phantom)] is designated spread-out Bragg peak or SOBP, as shown with a 15 MV X-ray beam for dose *vs* depth on the central axis in Fig. 3a and for cross section view in Fig. 3b. The depth spacing between Bragg peaks in the SOBP, required to produce the desired dose uniformity, varies with the energy spread in the primary beam and straggling in the beam path. It is typically of the order of 2–5 mm for protons. Due to less straggling in carbon beams compared to proton beams, ridge filters are employed in two ^{12}C ion centers in Japan to produce the spreads in Bragg peaks comparable to those of protons, and thus allow for increased spacing of the layers.

As evident from inspection of Fig 3, a ^{1}H beam delivers a near zero dose deep to the target for each proton beam path. This constitutes an unequivocal advantage for most treatment situations. Importantly, the integral total body dose by ^{1}H therapy is about half that of intensity modulated X-ray therapy [IMXT] as calculated by Lomax et al. [11]. For facilities equipped with gantries, planning for dose delivery of ^{1}H and for ^{12}C ion therapy has the same flexibility as for X-ray therapy in terms of beam number, direction, intensity modulation and image guided therapy. There is, however, a more stringent requirement for accurate dose delivery. An additional advantage for particle beam treatment is that fewer fields are required to create the desired dose distribution than for IMXT. The design of a SOBP for ^{12}C ion beams is more complicated than for protons because of the non-trivial task of correctly adjusting physical dose for the variation in RBE so as to have a flat biologically effective dose across the SOBP. This is discussed in the section on Radiation biological factors.

Fragmentation tails

A difference in dose distribution between ^{1}H and ^{12}C beams is the fragmentation tail of the ^{12}C beam as illustrated in Fig. 4. The tail develops from the fragmentation of the ^{12}C ions in the primary beam, due to their nuclear interactions with the atoms in the irradiated medium. These fragments are predominantly intermediate to low energy ions of boron, beryllium, lithium, helium with protons being the most numerous by a large factor [12,13]. Some of these fragments travel non-negligible distances beyond the range of the ^{12}C beam and deposit their energy in the "fragmentation tail". This is illustrated in Fig. 4 for 195 MeV, 281 MeV and 392 MeV ^{12}C beams. The tails are low physical dose and relatively high RBE with the net result being a low biologically effective dose in the fragmentation tail of ^{12}C beams [14,15] and Miller and Blakely, personal communi-

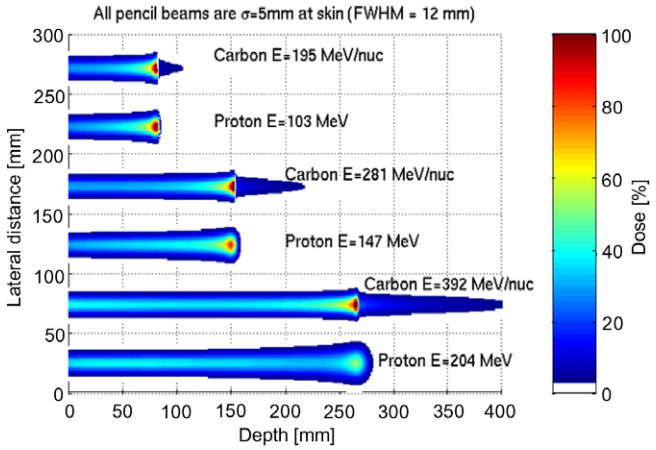

Fig. 4. Display of the penetration of fragmentation tails of 195 MeV, 281 MeV and 392 MeV ^{12}C beams. This contrasts with no tail for proton beams of energies of 103 MeV, 147 MeV and 204 MeV.

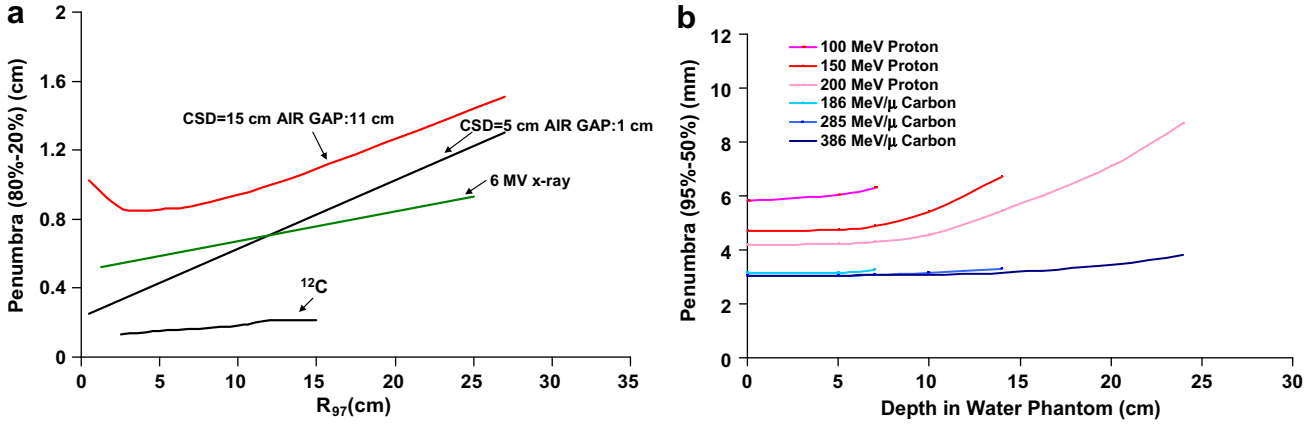

Fig. 5. (a) Penumbras are shown for passively scattered ^{1}H and ^{12}C ion beams. The penumbras of proton beams are plotted *vs* the R97 [depth to the 97% of maximum at the peak] [17] and the 290 MeV/μm ^{12}C ion [15] and the MGH 6 MV X-ray beams are plotted *vs* depth. Penumbra widths for the MGH passively scattered ^{1}H beams are modified by a 4 cm compensator and the air gaps are 1 cm and 11 cm. (b) Calculated 95–50% penumbra widths along the beam *vs* depths for very narrow, σ = 1.65 mm [FWHM = 4 mm] proton and carbon ion beams of three energies and ranges of ∼7 cm, 14 cm and 24 cm, personal communication from U. Weber, 2009.

cation, 2009. The fragmentation tails need to be explicitly included in the treatment planning systems to avoid unanticipated "Hot Spots" in adjacent critical normal tissues. Parallel to the ^{12}C ion beams are ^{1}H beams of the same penetration and no fragmentation tails are evident. There is a very low dose extension beyond the distal edge of the proton SOBP due to the production of secondary neutrons along the beam path. The dose at 2–13 cm past the distal edge of the SOBP was 2 to 0.6×10^{-3} mSv/Gy of the SOBP dose as determined by Wroe et al. [16].

Penumbra

The penumbra (penumbra [80–20%] is the width of the dose band lateral to the field edge for the dose to decrease from 80% to 20%) [80–20%] for a collimated passively scattered proton beam varies markedly with depth and is highly dependent on the physical design of the beam defining systems in the machine, collimating system and the air gap between the compensator and body surface. The impact of variations in these parameters on collimated passively scattered proton beams at the MGH proton therapy center [230 MeV accelerator] is demonstrated by the calculations and measurements of Safai et al. [17]. The size of the air gap and any variation in the gap across the field warrant special consideration in assessment of a treatment plan and in the monitoring of dose *vs* depth by any technique, *e.g.* with in beam PET. At MGH, clinical set-ups typically have compensator-to-surface distance (CSD) ⩽15 cm and air gap ⩽11 cm. Fig. 5a presents two sample curves from the paper of Safai et al. [17], *viz.* for air gaps of 1 cm and 11 cm and each with 4 cm plastic compensators: penumbras of beams at 10 cm depth increases from 6.4 mm to 9.6 mm, with this increase in air gap. At 25 cm depth the penumbras are ∼12 mm and 15 mm. In comparison, 6 MV X-ray beam penumbras at 10 cm and 25 cm depth are ∼6.7 mm and 9.3 mm, a smaller increase than for the passively scattered ^{1}H beams. There are special situations for which greater distances are necessary, *e.g.* treatment through the couch, requiring CSDs up to 25 cm and air gaps up to 21 cm, resulting in wider penumbras. Further, the penumbra increases with thickness of the range compensator. In comparison, the penumbras of passively scattered ^{12}C ion beams at Chiba are very narrow, *i.e.* ∼1.5–2.3 mm between 2 cm and 15 cm depth, Kanai et al. [15].

For active scanning, the beam size is a critical parameter. Namely, the average proton beam at PSI has been approximately σ = 8 mm [FWHM of ∼19 mm] as measured by Lomax et al. [18]. This has been reduced steeply by their new gantry system as indicated by this personal communication from Safai and Pedroni, 2010. "Recent measurements at Paul Scherrer Institute (PSI) on a gantry, specifically designed for proton scanning, can deliver very narrow pencil beams at isocenter for both high- and low-energy protons even without collimation. For instance, the PSI team has measured pencil beam sizes (sigma in air) close to 2 mm for 230 MeV protons (water-range of 33 cm) and 4.5 mm for 70 MeV protons (water-range 4 cm). Therefore, potentially, the penumbra (80/20) at the Bragg peak in water could be <5 mm up to about 15 cm water-depths and ∼8 mm at 30 cm". These results indicate that the penumbra of ^{1}H beams for active scanning at depths up to 15 cm may differ only marginally from the ^{12}C ion beams of today.

Uli Weber, personal communication, 2009, has provided the 95–50% penumbra widths along the beams and at the Bragg peaks for penetrations of 7, 14 and 24 cm for narrow [σ = 1.65 mm or ∼4 mm FWHM] proton and carbon pencil beams at GSI, Darmstadt, Fig. 5b. A clearly positive feature of clinical carbon beams is a more narrow penumbra than that of ^{1}H beams and this advantage increases with depth. As shown in Fig. 5b the ^{12}C ion penumbra width is essentially flat at ∼3–4 mm out to 24 cm depth because carbon ions have: (1) a factor of 6 higher charge, (2) a factor of 12 higher mass, and (3) require roughly a factor of two higher energy per nucleon for the same range in tissue than for protons. The primary beam broadening due to multiple Coulomb scattering is smaller roughly by a factor of 4 for ^{12}C ions resulting in the penumbra advantage, *e.g.* see Kramer et al. [19]. In contrast, the penumbra of narrow proton pencil beams increases toward end of range due to the greater scatter in tissue and this effect increases with depth [higher energy]. The ^{1}H penumbra widths on the beams from the new gantry at PSI indicate that the difference between PBS ^{1}H and ^{12}C ion out to 15 cm depth will be close.

Kempe et al. [20] have plotted the penumbra *vs* atomic number of the particle beam and showed a steep decrease, *viz.* a factor of ∼2 from proton to helium beams and then a more gradual decrease to neon.

Dose lateral to the penumbra

A very large component of the integral dose to the whole body for passively scattered beams is from the machine head while that from pencil beam scanning is scattered almost entirely from the beam in the patient. Measured doses at ∼10–50 cm lateral to the penumbra are slightly lower for passively scattered ^{1}H beams

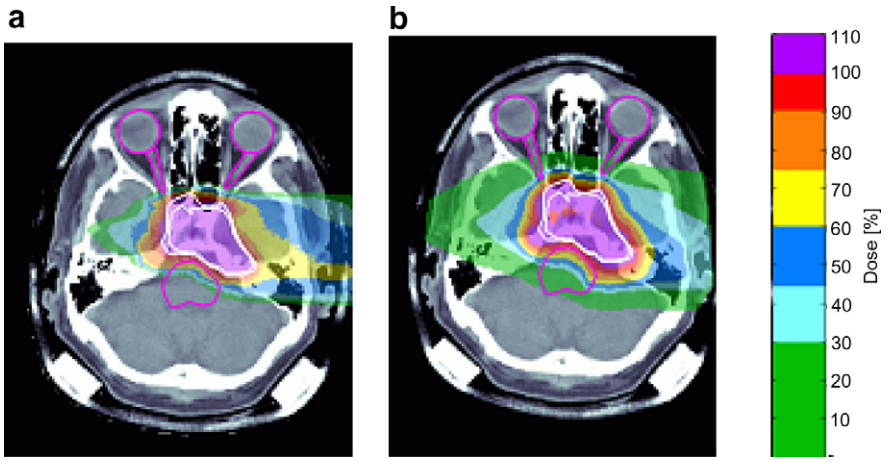

Fig. 6. (a) Treatments plans for a patient with a tumor of the skull base for actively scanned ^{12}C ion therapy: ^{12}C ion beams [O. Jaekel at DFKZ]. (b) Actively scanned ^{1}H beams [A. Trofimov at MGH].

[21–23] than intensity modulated X-ray therapy [24]. The lateral dose is lower for actively scanned [25] than passively scattered ^{1}H beams. The neutron dose lateral to a passively scattered carbon beam at Chiba at 50 cm has been reported to be ~0.2 mSv per Gy(RBE) to the SOBP and this is lower than that measured for their proton beams [26].

Heterodensities

A fact of physics is that varying tissue densities and atomic composition in the beam path are the determinants of the depth of beam penetration. That is, a structure of increased density, *e.g.* a bone, decreases the particle's physical range as an air cavity extends the physical range. Hence, heterodensities must be recognized and the energy distribution in the beam designed to correct for their impact on the actual dose distribution. Software for correction for the impact of heterogeneities in the beam path was first developed in 1978 by Goitein [27]. Urie et al. [28] developed the technique of compensator expansion (smear) to reduce the potential target under dosing due to internal motion of the target and set-up uncertainties. The compensator expansion, due to the uncertainties in the positioning of either hyperdense or hypodense structures, results in additional irradiation of tissues distal to the target.

To account for uncertainties in the density conversion to particle stopping powers, distal and proximal margins are added to the planning volume (for protons, the margins are, respectively, of the order of 3% of the depth to the distal and proximal edges of the target). Except for anatomic sites with extreme variation of density, *e.g.* bone interfacing with air as in the region of the nasal sinus, the corrections are clinically acceptable. In such situations, there are significant uncertainties that need careful attention in treatment planning as considered by Weber and Kraft [29].

Fig. 6 presents treatment plans for a patient with a head/neck tumor by actively scanned ^{12}C ion beams prepared by O. Jaekel at DFKZ and by actively scanned proton beams on the same patient by A. Trofimov at MGH. The volumes receiving high dose are quite similar for the two plans. The normal tissue volume irradiated to low doses is appreciably larger for ^{1}H treatment.

Other charged particles

There are positive charged particle beams with LET values intermediate between ^{1}H and ^{12}C that are of potential clinical interest, especially helium and lithium ions. Our consideration of high LET clinical particle beams is directed to ^{12}C ion beams as they probably provide the highest LET for clinical particle therapy with an acceptable dose in the fragmentation tails. For a review of the potential of other particle beams for clinical therapy see Ref. [20].

Radiation biological factors

Proton beams

Clinical proton beams are low LET radiations, *viz.* the biological effectiveness per unit of energy absorbed is very close to that of high energy X-rays. The ICRU (ICRU is the International Commission on Radiation Units) has recommended 1.10 as a generic RBE for proton therapy [30]. Essentially all proton therapy centers have adopted their recommendation. This RBE value of 1.10 is based principally on an analysis of the published RBE values determined on *in vivo* systems for clinically relevant dose levels and at the mid-SOBP by Paganetti et al. [31]. Accordingly, planning of proton therapy is comparatively straight forward, *viz.* employ this one value for all tissues, organs [partial or total], dose levels and observation times. Note that this RBE of 1.10 is less than the 1.15 for 250 kVp rays. The biological reality is that variations of proton RBE with tissue type and dose are likely as discussed by Gerweck et al. [32] *etc.*, but the variations are too small for accurate determination and application in the clinic.

Carbon ion beams

Planning the physical dose distribution from ^{12}C ion beams is substantially more complex than for ^{1}H beams because of their varying LET and associated RBE values.

RBE of tumor vs normal cells

Were high LET to provide a clinical advantage, one basis could be an inherently higher sensitivity of tumor than normal cells to high LET radiations, *i.e.* a higher RBE for tumor than normal cells irradiated under identical conditions. Substantial experimental data do not provide support such a differential sensitivity. Fig. 7a presents three sets of RBE determinations on tumor and normal cells irradiated *in vitro*. These are $RBE_{0.1}$ values for 62 MeV neutron irradiation of 30 cell lines by Warenius et al. [33] and for 13 keV/μm and 77 keV/μm ^{12}C ion irradiation of 16 cell lines by Suzuki et al. [34]. There were two normal cell lines in each of these two studies, *i.e.* a total of 4. These experiments were performed in a single laboratory for neutron studies and a single laboratory for the ^{12}C ion irradiation, *viz.* standard conditions for cell culture and scoring of colony formation. These results indicate no trend for a higher RBE for tumor than normal cell lines. Ando et al. [35] pre-

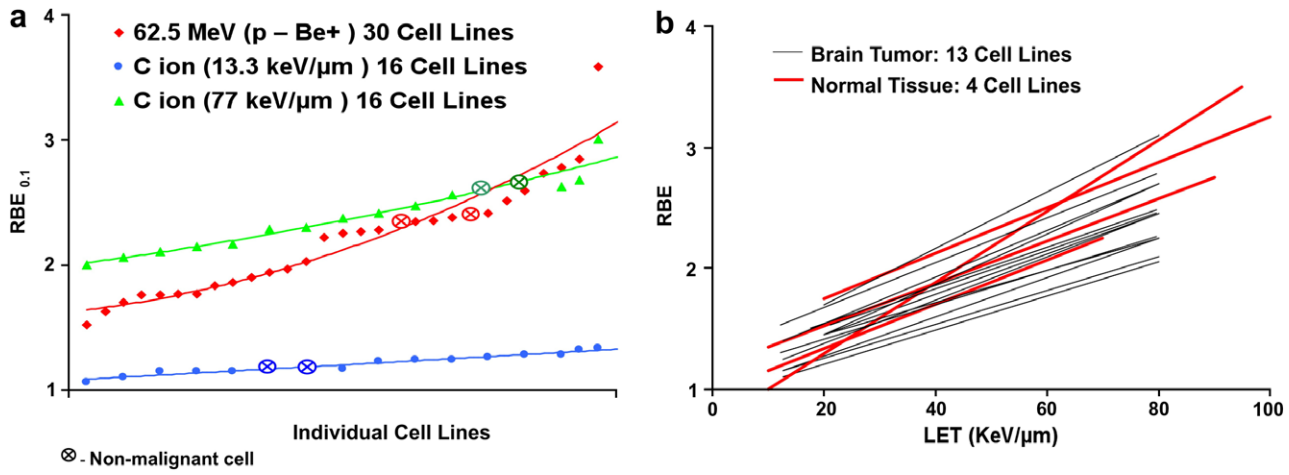

Fig. 7. RBE of tumor and normal cells *in vitro*. (a) Scattergrams of RBEs of 30 cell lines [two are normal cell lines] for 62 MeV neutron irradiation [33] and for 16 cell lines [two are normal cell lines] irradiated by ^{12}C ion beams at ~13 and ~80 keV/μm [34]. The large dots represent the normal cell lines. (b) RBE *vs* LET curves for 4 normal fibroblast cell lines and 13 brain tumor cell lines [35].

pared plots of ^{12}C ion $RBE_{0.1}$ *vs* LET for ^{12}C ion irradiation, ~13 keV/μm to ~80 keV/μm, for an extensive number of tumor and four normal cell lines. Fig. 7b presents the $RBE_{0.1}$ *vs* LET curves for 13 brain tumor and the 4 normal cell lines from their paper. The RBE curves were not higher for the brain tumor than the normal cell lines. The conclusion is that the experimental data do not support the concept of higher RBEs of tumor than normal cell lines irradiated under standard metabolic conditions. This provides an indication that were there higher RBEs for tumors, they would be based on differences in metabolic conditions, *e.g.* pO_2, possibly variation in radiation sensitivity with position in the cell replication cycle, and perhaps other factors. The clinical experience with neutron therapy is that there is a high RBE for late responding normal tissues [low α/β] evidenced by the increased frequency of late complications. High LET irradiation would be predicted to be more effective against slowly growing and low α/β tumors, *vide infra*.

Design of a clinical ^{12}C ion beam

Factors considered in the design of a ^{12}C ion clinical beam are the physical dose [Gy], RBE and dose in Gy(RBE). Fig. 8 demonstrates the variation in RBE and the complementary shift in physical dose across the 6 cm SOBP of a 290 MeV ^{12}C ion beam to achieve a uniform dose in Gy(RBE) in the SOBP. The estimated peak RBE in this example is 3.0 within an uncertainty band of 2.5–3.5. The red band around the RBE curve represents the uncertainty in RBE, and the blue band represents the uncertainty in Gy(RBE) across the SOBP. To achieve a uniform dose in Gy(RBE) across the SOBP, physical dose [Gy] is decreased as RBE rises. There is a steep fall in Gy(RBE) and physical dose at the distal edge of the most distal Bragg peak. Were the true RBE 3.5 not 3, the dose in Gy(RBE) delivered to the patient would be substantially higher than intended by some 16%. This merely emphasizes the potential impact of an error in RBE employed.

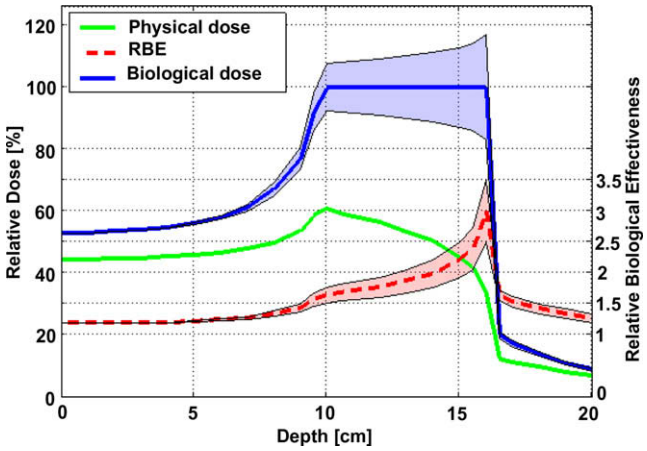

Fig. 8. Design of a 290 MeV ^{12}C ion beam with a 6 cm SOBP for an assumed maximum RBE of 3.0. The impact of an error in selecting the RBE were the true RBE in the range of 2.5–3.5 is represented by the uncertainty bands around the dose in Gy(RBE) across the SOBP.

Estimation of the clinical RBE is not simple or straightforward because of the poorly quantified impact of LET, dose, tissue type, fractionation, pO_2 and cell position in the cell replication cycle on the net clinical RBE at each point in the irradiated volume. Additionally, there is the critical fact that the experimentally determined RBE values are based on *in vitro* and *in vivo* laboratory systems. That is, there are no experimental data for human tissues and properly so.

RBE vs LET

RBE for most cell and tissue systems increases with LET over the ^{12}C ion LET range of ~40–100–150 keV/μm. A significant finding is that the effect of LET on RBE varies with the cell line. That is, for a specified LET of a defined particle beam, RBE values may vary widely between different cell lines, as demonstrated in Fig. 9 for V79, CHO and xrs5 cell lines irradiated by 270 MeV ^{12}C ion beams spanning a broad range of LETs, as reported by Weyrather et al. [36]. Of interest is that the major changes in LET and RBE occur predominately in the terminal 10 mm of particle range.

This is in accord with the considerable spread in RBE values shown in Fig. 7 for cell lines irradiated by beams of specific LETs. Further, the RBE of a defined LET and a particular cell line can vary significantly with the particle beam, as found in the study by Furusawa et al. [37].

RBE and dose

That RBE increases with decrease in dose of high LET radiation in the clinically relevant range has been extensively documented for cells *in vitro* and experimental animal tissues. The mechanism for this effect is largely the differences in the capacity of some cells and tissues to repair sub-lethal radiation injury, *viz.* sharply dimin-

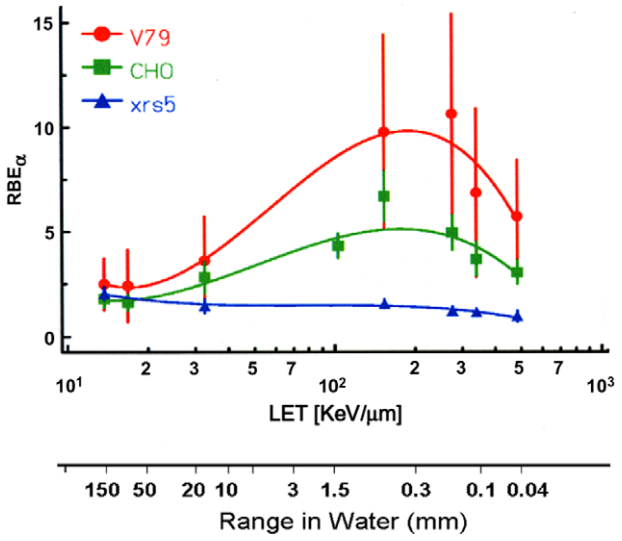

Fig. 9. The RBE *vs* LET for V79, CHO and xrs5 cell lines for 270 MeV ^{12}C ion irradiation. The lower abscissa gives the RBE *vs* residual range [36].

ished for high LET radiations. Here, two experiments on the response of late responding normal tissues to highly fractionated and high LET irradiation are briefly described. Karger et al. [38] analyzed frequency of paresis grade II in 346 female Sprague Dawley rats (360 animals entered the study, but 14 had to be sacrificed early with no evident spinal cord) damage leaving 346 for analysis of spinal cord injury following irradiation of a segment of the cervical-thoracic cord in 1, 2, 6 or 18 fractions on consecutive days and the animals followed for 300 days. The radiation beams were 15 MV X-rays and ^{12}C ion beams of LET of 13 keV/μm or 125 keV/μm, *viz.* in the plateau and in the 1 cm SOBP. Their endpoint was the dose that on average produces paresis in 50% of the animals, *viz.* the D_{50}. For the 125 keV/μm beam, the measured RBE for spinal cord injury increased from 1.8 to 5 [a factor of 2.8] as ^{12}C dose was decreased from 13.9 to 0.98 Gy/fraction. The RBE increase was quite steep for dose less than 3 Gy, as shown in Fig. 10. In comparison, RBE for the 13 keV/μm beam did not increase with decrease in dose per fraction from 17 to 3 Gy. This marked dependence of RBE on LET reflects the fact that at high LET, repair of radiation injury is much reduced.

Robbins et al. [39] reported similar results in experiments on normal kidneys of 111 pigs irradiated with 42 MeV neutrons or

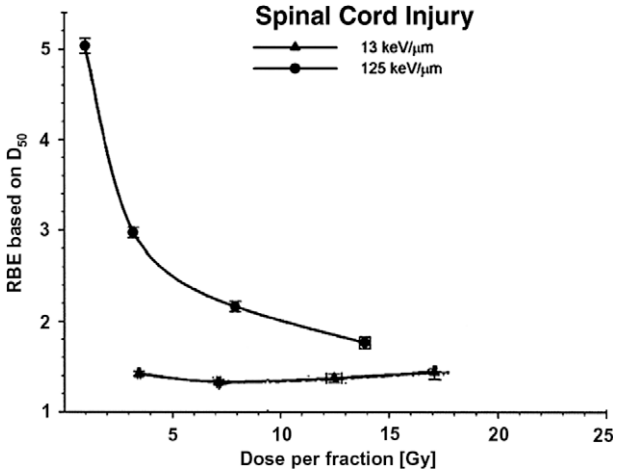

Fig. 10. RBE *vs* dose per fraction for late cervical spinal cord damage by ^{12}C ion *vs* 15 MV X-irradiation [38].

250 kVp X-rays in 1, 6, 12 or 30 fractions in 1 or 39 days (female pigs of 20–25 kg body weight). RBE [for intermediate effect] *vs* dose per fraction increased from 1.2 to 4.6, *i.e.* a factor of 3.8 as X-ray dose per fraction decreased from 7 to 1.3 Gy. That RBE of high LET radiations increases with decrease in dose below ~6–10 Gy is well established.

RBE vs OER

The radiation sensitivity of normal and malignant cells to low LET radiation varies by factors of ~2.5–3 as pO_2 is increased from <1 mm Hg to ~25 mm Hg, *i.e.* the OER or the ratio of dose to produce a defined response under hypoxic conditions to that for aerobic conditions is ~2.5–3 as reviewed by Hall and Giacci [40]. Measured pO_2 levels in many epithelial and mesenchymal tumors in experimental animals and human patients reveal the presence of hypoxic and, hence, relatively radiation resistant cells as demonstrated by Becker et al. [41], Brizel et al. [42] Nordsmark et al. [43] and Parker et al. [44]. OER is reduced with high LET radiation. Thus, a predicted gain from high LET radiation therapy is a lesser impact of hypoxic cells on TCP. A plot of OER [$SF_{0.1}$] *vs* LET for human salivary gland cells *in vitro* by Furusawa et al. [37] has shown that OER is relatively flat at ~3 over the LET range from 1 to ~40 keV/μm and then declines to ~2.2 at ~80 keV/μm, approximately the LET for mid-SOBPs of ⩾6 cm. OER further declines to ~1.2 at ~200 keV/μm, Fig. 11a. RBE increases with LET in a near complimentary manner to the decline in OER. The two curves cross at RBE ~2.3 and LET ~70. Blakely et al. [14] demonstrated that for T-1 human kidney cells the decline in OER occurs predominately in the final 1 cm of range and then increases back to near normal levels at the start of the fragmentation tail, Fig. 11b. Blakely et al. [45] then measured the OER to be 2.2 and 2.6 at the mid-point of 4 and 10 cm SOBPs of ^{12}C ion beams with ranges of 14 and 24 cm.

Thus, the benefit of clinical ^{12}C ion beams due to a reduced OER would be predicted to be modest as the LET at mid-SOBP of SOBPs of ~6–12 cm would yield an OER of >2.2, *viz.* higher than that of fast neutrons.

RBE vs cell position in the cell replication cycle

Radiation resistance of actively dividing cell lines to X-irradiation is increased in late S phase cells relative to G1 and M phases. However, S phase is not a large segment of the cell replication cycle of tissue cells, especially in the slowly proliferating cells of the late responding tissues. Further, any gain by this mechanism is limited by the fact that the LET over the SOBP of a clinical ^{12}C ion beam is sufficient to effect only a modest change in the variation of sensitivity with position in the cell replication cycle. See discussion in the books of Hall and Giacci [40] and Raju [46].

RBE for cell transformation

RBE values from *in vitro* experiments reported for transformation of cells relative to that for cell kill in culture have been variable. For instance, Miller et al. [47] reported RBE_α values for cell survival and for transformation of C_3H $10T^{1/2}$ cells irradiated by 250 kVp X-rays or by neutrons of 10 energy levels, 0.04–13.7 MeV. RBE_αs for transformation was consistently equal to or marginally lower than for cell kill. In other reports, the RBEs for transformation have been substantially higher for transformation, *e.g.* Han et al. [48], Bettega et al. [49].

Clinical results of particle beam radiation therapy

A definitive assessment of the relative clinical efficacy of ^{1}H and ^{12}C ion therapy cannot be made on the basis of published data

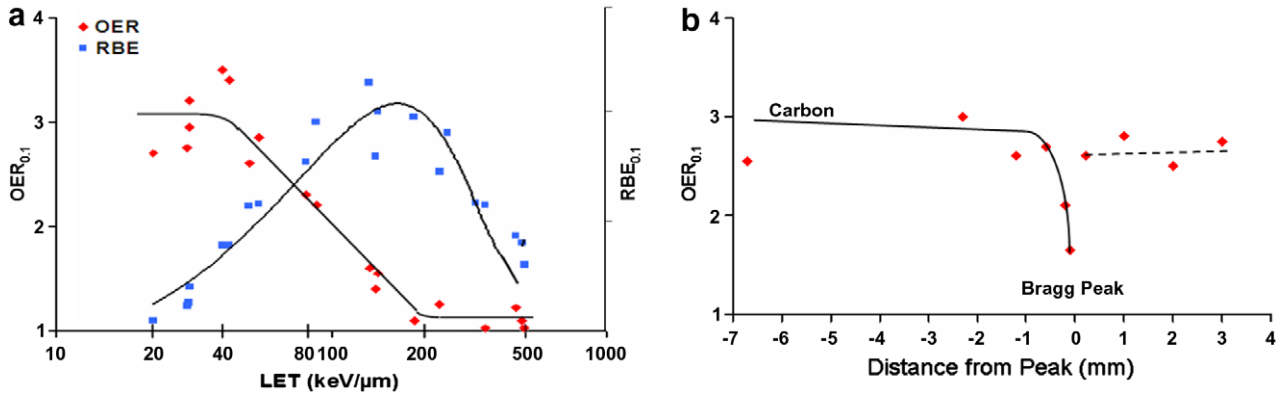

Fig. 11. (a) OER and RBE *vs* LET for HSG tumor cell line *in vitro*. [37]. (b) OER *vs* depth near the end of range and over the fragmentation tail of a ^{12}C ion beam for T-1 kidney cells. [14].

as there are none from clinical trials of ^{1}H *vs* ^{12}C ion therapy. The need for such data is clear with the expanding number of ^{1}H and ^{12}C ion treatment facilities. There has been an extensive experience with high LET radiation therapy *viz.* with fast neutron beams. This will be considered and then the outcome data of ^{1}H and ^{12}C ion therapy assessed.

Fast neutron therapy was the first high LET radiation therapy

Several studies of fast neutron beam therapy [high LET beams] *vs* X-ray beams that featured near comparable depth dose characteristics are considered here. Depth dose curves are similar for 12.5–16 MeV neutron *vs* 250 kVp X-rays, 40–50 MeV neutron *vs* ^{60}Co and 62–66 MeV neutrons *vs* 4–10 MV X-rays.

The initial clinical use of fast neutrons was in 1938 by Stone at the University California at San Francisco and at Berkeley. This was only 6 years after the discovery of the neutron by J. Chadwick. In 1946, Stone presented the status of the 249 treated patients at 4–9 years post-hypofractionated neutron therapy [50] and concluded that that his results were not satisfactory.

Catterall et al. [51] reported in 1977 from the Hammersmith Hospital, London that of 133 patients with locally advanced head/neck cancers randomly assigned to 15.6 Gy neutrons (the mean neutron energy was 7.5 MeV) in 12 fractions/4 weeks and to 45.4 Gy X-rays/12 fractions/4 weeks or up to 68.6 Gy/30 fractions/43 days by ^{60}Co photons or linear accelerator X-rays local control was obtained in 76% and 19% for unspecified times periods. Only 40% of the photon patients were treated at Hammersmith. Severe complications were noted in 10 and 2 patients, respectively. The exceptionally low TCP in the X-ray patients was not explained. Stafford et al. reported in 1992 [52] that 38 of their H/N patients treated by fast neutrons at Hammersmith Hospital (These included: airway obstruction, intractable dysphagia, osteoradionecrosis and others) had developed serious complications at a mean time of 5.5 years. These were described as more severe and frequent than in his X-ray treated patients.

One impressive result of neutron therapy at the Hammersmith Hospital reported by Blake et al. [53] was compete regression of 71% of 87 malignant melanomas.

Stimulated by the reported positive tumor regression and local control results at Hammersmith Hospital, a substantial number of neutron therapy centers were established around the globe. Strong motivating factors to study neutron therapy were that many human tumors have hypoxic foci and the OER for high LET irradiation is reduced and that repair of radiation injury is less for high LET irradiation. Two Phase III trials are mentioned. The Edinburgh trial was based on 165 patients with locally advanced squamous cell carcinomas of the head/neck treated in 20 fractions in 4 weeks by 15 MeV neutrons to 15.6–16.7 Gy or by X-ray beams to 54–56 Gy (the neutrons were produced by 15 MeV deuterons on beryllium and 125 cm TSD and the X-rays were 4 MV and 100 cm TSD). The 5 year local control rates were 44% and 45%, respectively, as reported by MacDougall et al. in 1990 [54]. Dose distributions were judged comparable for the neutron and X-ray treatment plans for these head/neck lesions. Of serious concern were the seven fatal complications in the neutron but none in the X-ray treated patients. Maor et al. reported in 1995 on 169 patients entered into a multi-institutional trial of neutron therapy of patients with advanced squamous cell carcinoma of the head/neck. Treatment was 20.4 Gy by neutrons in 12 fractions in 4 weeks *vs* X-rays at 70 Gy in 35 fractions in 7 weeks. Local–regional control rates at 3 years were 37% and 32%, respectively, for neutrons and X-rays. However late grade 3–5 toxicities were 40% and 18%, respectively [55].

In contrast, Phase III trials have shown TCP gains in patients who had with similar tumors and who respired O_2 at 3 ATA at dose fraction. See the review of this field by Overgaard [56] Thus, despite a lower OER and the presence of hypoxic regions at some frequency in these locally advanced SCCs [41–43], neutron therapy has not been documented as yielding an appreciably higher TCP than X-ray therapy. Even if discounting the higher frequencies of normal tissue injury, no important clinical gain in tumor control probability has been achieved by neutron therapy for SCCs of the head/neck region.

Early neutron trials of fast neutron therapy for prostate cancer gave mixed results. The NTCWG [23–85] trial of 172 evaluable patients with T3–4 No-1or high grade T2 [Gleason $\geqslant$6] prostate cancer were treated by neutrons to 20.4 Gy at 1.7 Gy per fraction three times/week or X-rays to 68–70 Gy [1.8–2 Gy per fraction] and reported by Lindsley et al. [57]. The 5 year "histological failure" rates for neutron *vs* X-ray treatment were 13% *vs* 32%. However, the 5 year survival rates were 68% *vs* 73%, *viz.* no survival gain for neutron therapy. Prostate cancers have been shown to have hypoxic cells by electrode measurements of Parker et al. [44].

Local control of salivary gland tumors by fast neutron therapy appears to be improved over that by X-rays. The RTOG and MRC clinical trial, based on a total of 25 patients, with locally advanced carcinoma of the parotid gland had 10 year local control rates of 56% and 17% for neutrons and X-rays but no gain in overall survival, *i.e.* 15% *vs* 25%, as reported by Laramore et al. [58]. The pooled local control result of 267 patients in nine studies of neutron irradiation of salivary gland tumors was 68% as reviewed by Griffin et al. [59] *viz.* higher than nearly all results reported for X-ray ther-

apy. The available data do not provide information as to the TCP for a defined late NTCP. We note that CC Wang used two fractions per day X-irradiation of 14 locally advanced parotid glands carcinomas and obtained a 5 year actuarial local control of 82% [60].

Wijffels et al. [61] examined for presence of hypoxic cells in seven resected parotid gland carcinomas by a broad spectrum of assays. They found no evidence of hypoxic regions in any of the seven tumors, *i.e.* no support the expectation that the reduced OER of neutron beams would contribute to local control of salivary gland tumors.

Laramore and Griffin [62] reviewed the status of fast neutron therapy and suggested that there was adequate potential for gains to merit further study of neutron therapy for patients with carcinomas of the salivary glands, pulmonary apex tumors, prostate and sarcomas of soft tissue and bone. Duncan [63] also assessed the outcomes of the experiences in fast neutron therapy and concluded that the evidence for a significant gain had not been presented.

The opinions of a high proportion of clinicians active in neutron therapy have been that neutron therapy did not yield clinical gains, *viz.* unimpressive local control rates and serious incidence of late complications. Of the eight neutron therapy centers that have been operational in the US (the six centers that have closed are: Cleveland Clinic, MD Anderson Cancer Center, US Naval Research Laboratory, Washington, DC, University of California at Los Angeles, University of Pennsylvania and Harpers Hospital), only two are currently active, University of Washington, Seattle and the Fermi National laboratory [G. Laramore; T. Krock, personal communication, 2009]. The number of centers in Europe has decreased to two: an accelerator based unit at Essen, that is irradiating ~10 salivary gland tumors per year [Wolfgang Sauerwein, personal communication, 2009] and the fission neutron program at the MEDAP reactor in Munich. This is used for superficial lesions as the 50% depth dose is at 5.4 cm, Wagner et al. [64]. The center in South Africa continues in active operation [Dan Jones, personal communication, 2009]. Present interest in high LET radiation is predominantly for ^{12}C ion beams.

^{1}H and ^{12}C ion clinical studies

Selected reports of clinical outcome for ^{1}H, ^{12}C ion and X-ray therapy are considered here in terms of TCP, NTCP and BED. The clear emphasis is on reports of ^{1}H and of ^{12}C ion radiation therapy of the nine tumor types under review. The tumors considered are chordomas and chondrosarcoma of skull base, and chordoma of sacrum, uveal melanoma, squamous cell carcinomas [SCC] and adenocystic carcinomas [ACC] of the head/neck region, early stage non-small cell lung cancer [NSCLC], hepatocellular carcinoma [HCC] and prostate carcinoma.

As noted earlier, there is a major difference in dose fractionation between the ^{1}H and ^{12}C ion treated patients, *viz.* the conventional 1.7–2.1 Gy(RBE) per fraction [for most tumors] and hypofractionation of 3–14 Gy(RBE) per fraction. To compare different fractionation protocols, we have employed the linear quadratic model [65] to compute the BED or the estimated biologically equivalent dose of X-irradiation given at 2 Gy per fraction predicted to produce the same response as the altered fractionation schedule. The BED values in Tables 1–7 have been computed according to the equation $\mathrm{BED} = nd \times [(\alpha/\beta + d) \div (\alpha/\beta + 2)]$. The symbols are: n = number of equal dose fractions; d = dose per fraction. The α/β is derived from laboratory data according to the formula: $S = e^{-\alpha D - \beta D}$. The symbols are: S is the survival fraction at single dose D, α and β are constants. The α/β is ratio is the dose at which the linear and quadratic contributions to the cell kill are equal.

That there are significant uncertainties in key parameters in the calculation of BEDs, *e.g.* RBE [dependent on dose/fraction and the specific tissue] and α/β values [quite variable between different tissues] is well recognized [66–68]. Despite the lack of data for quantitating these variables for human tissues, BEDs are judged useful in providing a defined system for estimating the effect of different fractionation schedules. There is real uncertainty as to the range of dose per fraction to which this model may be usefully applied in calculating a BED. An additional uncertainty is that BED calculations do not take into account differences in time between fractions or overall treatment time. After careful consideration, our policy is to use doses per fraction in the range of 1–8 and make no allowance for time. However, there are highly informed opinions that have judged the upper limit to be ~5, ~10 or ~18 Gy based on data from cells in culture and from animal data *in vivo*, Joiner and Van der Kogel [69], Kirkpatrick et al. [70] and Brenner [71]. The use of Gy(BED) is discussed in text books on radiation oncology, *e.g.* Gunderson and Tepper [72], Halperin et al. [73], Peckham et al. [74] among others and to include no factor for time of treatment. The α/β values employed are two for chordoma of skull base and sacrum. chondrosarcoma of skull base [75], and prostate carcinoma [76,77]; 10 for NSCLC [78] and squamous cell carcinoma of the head and neck [79] and 15 for primary hepatocellular carcinoma and 10 for regional metastatic HCC regional nodal disease [80,81]. BEDs were calculated for adenocystic carcinoma at an arbitrary $\alpha/\beta = 10$; no reference was found. The BED value was not calculated for mucosal melanomas as we have only minimal experience with these tumors and no reference was located. The doses in Gy(RBE) given in the Tables are taken directly from the publications.

Almost all published clinical data on proton and carbon therapy have been generated from patients treated by passively scattered beams. The exceptions are the actively scanned ^{1}H beam therapy at Paul Scherer Institute [PSI] near Zurich and the ^{12}C ion beam at Gesellschaft für Schwerionenforschung [GSI] at Darmstadt. The latter has been transferred to the just opened ^{1}H and ^{12}C ion therapy center at the University of Heidelberg.

Doses for the different tumors are listed in Tables 1, 2 and 4–7 in Gy(RBE) and BED and the α/β value used. For the text, doses are given only in BED. BEDs were not estimated for radiation treatment of uveal melanomas and for stereotactic radiation therapy of NSCLC due to the dose per fraction >8 Gy(RBE).

Skull base chordoma

Effective treatment of skull base sarcomas by surgery and/or conventional photon therapy has been quite constrained by the extremely narrow or non-existent margins between tumor and critical CNS structures. This has meant that a high proportion of surgical resection specimens have microscopically or grossly positive margins. Similarly, radiation dose by conventional X-ray therapy has been limited to marginally effective doses. ^{1}H and ^{12}C ion beam therapy permits higher target doses at a relatively low risk of high grade CNS or other injury.

Four and five year local control results of ^{1}H ± X, ^{12}C ion and X-ray treatment of skull base chordoma are listed in Table 1. These ranged from 50% to 100% for doses of 64–96 Gy(BED). TCPs for ^{1}H ± X-irradiation were 54–59% for 65–68 Gy(BED) in 115, 100 and 33 patients by Terahara et al. [82]; Noel et al. [83,84], Hug et al. [85]. At 72 Gy(BED) delivered by actively scanned proton beams, Ares et al. [86] achieved a local control rate of 81% in 42 patients. The GIII complication rate was 6%, higher than in the other ^{1}H series and the ^{12}C series. Debus et al. [87] obtained a TCP at 5 years of 50% by X-irradiation to 64 Gy(BED). Thus, for low LET radiation the indication is an increase in TCP with dose over this range. The TCPs for hypofractionated ^{12}C ion irradiation at 70 Gy and 75 Gy(BED) were 60% and 63% at Chiba by Hasagawa et al. [88] and at Darmstadt by Schulz-Ertner [89]. Then at 88 and

Table 1
Skull base chordoma.

Beam	# Pts	Dose Gy(RBE)	Dose/Fx Gy(RBE)	BED Gy $\alpha/\beta = 2$	Local control at years	Late ⩾GIII injury	Reference
^{1}H	115	69	1.8	66	59% at 5	Not given	Terahara et al. [82]
^{1}H	100	67	1.9	65	54% at 4	GI–IV: 42%	Noel et al. [83]
	90					⩾GIII: 6%	Noel et al. [84]
^{1}H	33	72 [67–79]	1.8	68	59% at 5	GIII–IV in 4 [7%]	Hug et al. [85]
^{1}H[a]	42	74	1.9	72	81% at 5	GIII in 4 in 64 patients [6%]	Ares et al. [86]
^{12}C	10	52.8	3.3	70	60% at 5	GIII none	Hasegawa et al. [88]
	19	60.8	3.8	88	91% at 5		
^{12}C[a]	84	60	3.0[a]	75	63% at 5	GIII in 5 [5%]	Schulz-Ertner et al. [89]
	12	70	3.5	96	100% at 5		
X[b]	37	67	1.8	64	50% at 5	Serious in 1 [3%]	Debus et al. [87]
X	18	16 at Margin 33 at Max	1 Fx		53% at 5	None	Martin et al. [91]

[a] This series treated by active scanning pencil beam technique.
[b] Seven fractions per week.

Table 2
Skull base chondrosarcoma [Low-Intermediate Grade].

Beam	# Pts	Dose Gy(RBE)	Dose/Fx Gy(RBE)	BED Gy $\alpha/\beta = 2$	Local control at years	Reference
^{1}H	200	72	1.9 [1.8–2]	70	99% at 5	Rosenberg et al. [92]
^{1}H	25	69	1.8	66	75% at 5	Hug et al., [85]
^{1}H [PBS]	22	68	1.9 [1.8–2]	66	94% at 5	Ares et al. [86]
^{12}C	54	60	3.0	75	90% at 4	Schulz-Ertner et al. [93]
X	10	16; 33[a]	16		80% at 5	Martin [91]

[a] Median dose to margin and maximum dose.

Table 3
Uveal melanoma.

Beam	# Patients	Dose Gy(RBE)	Dose/Fx Gy(RBE)	Local control at years	Eye loss[a] due to eye injury (%)	Reference
^{1}H	2069	70	14	95% at 15	8	Gragoudas et al. [97,98]
^{1}H	2435	60	15	95% at 10	3[b]	Egger et al. [99,100]
^{1}H	1406	60	15	96% at 5	8	Dendale et al. [101]
^{12}C	57	70 [60–85]	14	97% at 3	5	Tsujii et al. [102]
X	133	60	12	98% at 2.9	13	Dieckmann et al. [103]
	25	70	14			

[a] These eye loss are not actuarial but the proportion of treated patients who had enucleation for treatment complication.
[b] The rate of eye loss due to radiation injury was reported in the 2003 paper. The enucleation rate in the 1203 eyes treated in recent period of 1994–1999 3%, lower than in the earlier periods [81].

Table 4
Head and neck cancers.

Beam	# Pts	Dose Gy(RBE)	Dose/Fraction Gy(RBE)	BED Gy $\alpha/\beta = 10$	Stage	Local control at years	Late ⩾GIII injury	Reference
Squamous cell carcinoma								
$^{1}H + X$	29	76	1.7	74	Stage I–IV	88%[a] at 5	3 Pts	Slater et al. [104]
	16				Stage III–IV			
^{12}C	15	57.6 or64	3.6 or 4.0	70 [65–75]	Advanced	56% at 5	None	Mizoe et al. [105]
Adenocystic carcinoma								
$^{1}H + X$	23	76[b]	~1.6	70	Advanced	93% at 3	4 Pts	Pommier et al. [106]
^{12}C	90	57.6–64	3.6 or 4.0	70 [65–75]	Advanced	79% at 5	None	Mizoe et al. [105]
$^{12}C + X$	29	72	X 1.8×30 ^{12}C 3.0×6	72	Advanced	78% at 4	2 Pts	Schulz-Ertner et al. [107,108]
X	34	66	1.8	65	Advanced	25% at 4	2 Pts	
Mucosal malignant melanoma								
^{12}C	72	52.8–64	3.3–4			84% at 5	0 Pts	Yanagi et al. [111]

[a] The local control rates were 4/4, 8/9, 9/10 and 6/6 for stages T1, T2, T3 and T4, respectively.
[b] The dose fractionation for 19 patients treatment was two fractions per day and one fraction per day in 4 patients.

Table 5
Non-small cell lung cancer.

Beam	# Pts	Dose Gy(RBE)	Dose/Fx Gy(RBE)	Stage	BED Gy $\alpha/\beta = 10$	Local control at years	Late GIII injury	Reference
^{1}H	68	51 or 60	5.1 and 6	T1 T2	72 [64–80]	87% at 3 49% at 3	None	Bush et al. [112]
^{1}H	17 20	82 [70–94]	4.2 [3.5–4.9]	T1A T1B	97 [79–117]	100% at 2 90% at 2	None 3 Lung [15%]	Nihei et al. [113]
^{1}H	11 10	66[a]	6.6	T1A T1B	91	100% at 2 90%[b] at 2	None	Hata et al. [114]
^{12}C	50	72	8	T1A T1B	108	~98% at 2 95% at 5[c]	1 Skin	Miyamoto et al. [115]
X	70	60 66	20 23	T1 T2		88% at 3	Lung peripheral 5/48 [10%] Lung Central 6/22 [27%];5 GV	Fakiris et al. [116] Timmerman et al.[d] [117]
X	20	54 [45–60]	18 [12–18]	T1,2		95% at 2	None [3Rib Fx, asymptomatic]	Ng et al. [118]
X	40	45	15	T1,2		85% at 2	38% had moderate/severe deterioration of lung function	Hoyer et al. [119]
X	19 12	45[e]	15	T1 T2		78% at 3.0 40% at 3.0	2 of 31 patients	Koto et [120]

[a] Three patients received 55 Gy(RBE). The doses were given as Gy and we converted them to Gy(RBE).
[b] This local failure developed in one of the three patients who received 55 Gy(RBE). The other 18 had 66 Gy(RBE).
[c] Local recurrence is defined as the first recurrence (Table 4).
[d] There were five Grade 5 [fatal] toxicities.
[e] Patients whose tumors were very close to a critical organ, received 60 Gy in eight fractions.

Table 6
Hepatocellular carcinoma.

Beam	# Pts	Dose Gy(RBE)	Dose/fraction Gy(RBE)	Size	BED Gy $\alpha/\beta = 10$	BED $\alpha/\beta = 15$	Local control at years	Late G $\geqslant$III injury	Reference
^{1}H	51	66	6.6	88% $\leqslant$5 cm	91	84	88% at 5	1 Lung	Fukumitsu et al. [123]
^{1}H	162	72 [52–88]	4.5	83% $\leqslant$5 cm	87	83	87% at 5	5 with $\geqslant$GII	Chiba et al. [124]
^{12}C	24 34 24 38 47	65 [50–80] 62 [54–70] 53 [48–58] 50.4 [48–53] 52.8	4.3 5.2 6.6 12.5 13.2	5 cm 3.7 cm 3.1 cm 4.6 3.7	77 79 73	74 74 67	81% at 5 86% at 5 86% at 5 89% at 5 96% at 5	↑CP $\geqslant$2 25% 29% 18% 13% 10%	Kato et al. [125]
X	23	66	2	<5 cm or 2 nodules $\leqslant$3 cm	66	66	19/25 at 2.4	GIII in 4	Mornex et al. [126]

Table 7
Prostate carcinoma.

Beam	# Pts	Dose Gy(RBE)	Dose/Fx Gy(RBE)	BED Gy $\alpha/\beta = 2$	Stage	Local control or bNED years	Late G $\geqslant$III injury	Reference
X + ^{1}H	96	67.2	1.9 [1.8; 2.1]	66	T3–4, Nx, N0–2, M0	Local control 81% at 5	Urethra 2% Rectal 2%	Shipley et al. [127]
X	93	75.6		74		92% at 5	Urethra 4% Rectal 9%	
$^{1}H \pm X$	1255	74	2	74	T1a–3	bNED at 5 75%	$\geqslant$GIII 1%	Slater et al. [128]
X + ^{1}H	197	70.2	1.8	67	T1b–2b	bNED at 5 61%	GU 2% GI 1%	Zietman et al. [129]
	196	79.2	1.8	75		bNED at 5 80%	GU 1% GI 1%	
^{12}C	295	64.5 [63;66]	3.2 [3.15;3.3]	84 [80;88]	T1,2	bNED at 5 92%	None	Tsuji et al. [130]
X	203 255 103	81	1.8	77	Prognostic Group Favorable Intermediate Unfavorable	bNED at 8 85% 76% 72%	$\geqslant$GII 8 years Rectal 1.6% GU 15%	Zelefsky et al. [131]

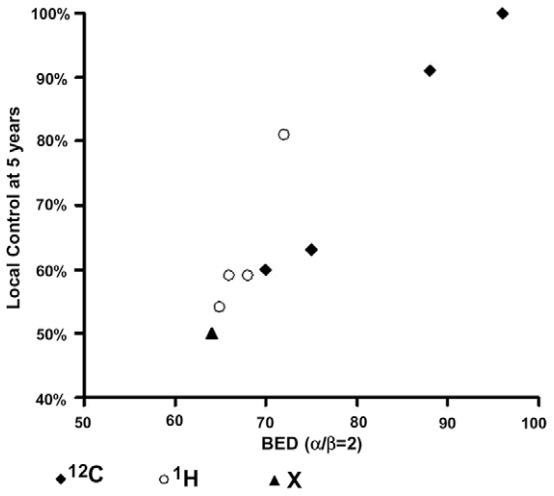

Fig. 12. Local control at 4 or 5 years for X, ^{1}H and ^{12}C ion irradiation of skull base chordomas *vs* BED, $\alpha/\beta = 2$.

96 Gy(BED) the local controls increased steeply to 91% and 100% for the two centers, respectively. Note that there were only 9 and 12 patients in these two very high dose groups. The incidence of GIII complications were none and 5% in the two ^{12}C ion series, *i.e.* lower than for the proton series. However, the frequency of GIII injury in 75 and 96 Gy(BED) groups from Darmstadt were not given separately for dose group. A plot of local control at 5 years *vs* BED for ^{1}H and ^{12}C ion irradiation is presented in Fig. 12. There is overlap of the ^{1}H and ^{12}C ion values over the BED range of 67–74 Gy. Due to the very small number of patients for 88 and 96 Gy(BED) dose levels, their position in this plot has greater uncertainty than the other points (the standard S shape of the dose response curve on a linear–linear grid is progressively less steep for TCP >85–90%; this is not evident here). Further, the data indicate a lower NTCP in the ^{12}C ion than in the ^{1}H treated patients. The implication of the more favorable TCP to NTCP relationship for ^{12}C ion than ^{1}H therapy is that either there is an RBE differential that favors ^{12}C ion irradiation of tumor or that the lower NTCP is due to superior dose distribution and or a more narrow CTV.

Although local control rates have not been published, Miyawaki et al. [90] examined the frequency and severity of brain injury in 59 patients treated by ^{1}H or ^{12}C ions for head and neck cancers at Hyogo Ion Beam Center. They found GIII brain injury in 0 of 48 ^{1}H treated patients and 2 of 11 ^{12}C ion treated patients by the CTCAE scoring system. For the Lent-Soma scoring the results were 1 of 48 and 1 of 11, respectively. The tumor types in their study were ACC 17, chordoma 9, SCC 7, malignant melanoma 7 and 19 other types.

Single dose photon irradiation for selected lesions achieved a 5 year local control results of 53% as reported by Martin et al. [91].

Skull base chondrosarcoma

Local control results of ^{1}H irradiation of chondrosarcoma are higher than for chordoma, as shown in Tables 1 and 2. Chordomas and chondrosarcomas of the skull base were similar with respect to anatomic site, size, dose distribution, prior surgery and managed by the same medical, physics and technician teams. The MGH 5 year ^{1}H local control rate for 200 skull base chondrosarcoma patients at 70 Gy(BED) was reported at 99% by Rosenberg et al. [92] as compared to 59% at 66 Gy(BED) for 115 chordomas [82]. This difference in dose could account for some difference but not likely the entire difference. In two additional ^{1}H series of 25 and 22 chondrosarcoma patients, local control results were 75% and 94% at 66 Gy(BED) [85,86]. By comparison, the ^{12}C ion TCP at 75 Gy(BED) was not as high as for the ^{1}H treatment, *viz.* 90% for 54 patients [93] *vs* 99% for 200 patients.

Data on incidence of severe treatment related injury were not given separately for chordoma and chondrosarcoma patients in the reports on local control for the two tumor types and are accordingly included those listed in Table 1. The frequency would be predicted to be the same in patients who received the same dose to the same volumes of normal tissues.

Sacral chordoma

Imai et al. [94] reported a 5 year local control rate of 89% in their series of 38 patients with unresectable sacral chordomas treated by ^{12}C ions 113 Gy(BED) in 16 fractions. The mean target volume was 520 ml. Thirty patients had primary and eight had post-surgical recurrent chordomas. Local control was defined as control within the PTV. Thirty patients had primary and eight had post-surgical recurrent chordomas. Treatment related morbidities in the 30 primary tumor patients were: four severe skin reactions [two requiring grafting]; one pelvic fracture and severe and permanent neurologic impairment in three patients, *i.e.* 8 in 30 patients.

DeLaney et al. [95] at the MGH treated nine patients with sacral chordoma by radiation alone using a combination of ^{1}H and X-ray beams to 74 Gy(BED). There were five primary and four post-surgical recurrent tumors. Local control was achieved in eight of the nine and the one local failure occurred a patient treated for recurrent chordoma. Several of the local controls have been followed for 5–10 years [unpublished data, Delaney, 2010]. Two of these patients have two GIII late radiation injury: one sacral neuropathy at 5.5 years and one erectile dysfunction at 3 years. They also treated 20 patients by surgery combined with radiation. The 5 year actuarial local control rate for the entire 29 patients was 87%. Rutz et al. at the Paul Sherrer Institute obtained 100% local control at 3 years in 13 patients with spinal and sacral chordomas treated by surgery [no titanium implants] and ^{1}H beams with variable margin status. In contrast, there were five local control failures in the 13 patients who had titanium implants [96]. The use of metallic implants is infrequent in resection of sacral sarcomas.

Uveal melanoma

The first treatment of a patient for uveal melanoma by protons was in 1975 by the collaborative effort of the MGH, the Massachusetts Eye and Ear Infirmary [MEEI] and the Harvard Cyclotron Laboratory [HCl]. As the lesions were small and the target position defined to unusual accuracy, we rapidly escalated the dose to 5×14 Gy(RBE) or 70 Gy(RBE). The five treatments were given on a daily basis. Results from Gragoudas et al. [97,98] for ^{1}H beam irradiation of 2069 patients with uveal melanoma have been very good, *viz.* local control rates of 95% at 15 years. Results are similar from Eggers et al. [99,100] and Dendale et al. [101]. The total number of patients treated at these three centers was 5910. Tsuji et al. [102] have obtained a local control rate of 97% at 3 years in 57 patients by ^{12}C ion therapy. Of clear relevance to this consideration is the report by Dieckmann et al. [103] of a local control rate of 98% in 158 patients at 2.9 years treated by stereotactic X-rays to 60–70 Gy in five fractions. These TCP values are given in Table 3 and all are at near maximum and do indicate an impressive accuracy in positioning of the melanoma on the beam in centers in the US, Europe and Japan and the effectiveness of the doses employed. The question is not if the TCP for 70 Gy(RBE) in five fractions to a specific tumor type and size would be the same for particle or X-ray beams, but rather the relative late NTCPs. Enucleation rates were 5–8% for ^{1}H and ^{12}C ion treatment but 13% in the X-ray treated patients, indicating an advantage of particle beam therapy. Note that the

X-ray treatment results are based on follow-up data at 2.9 years. The 15 year local control of 95% is about as high by radiation alone as achieved for any tumor.

Head and neck cancers

Results for squamous cell carcinomas [SCC], and adenocystic carcinomas [ACC] are given in Table 4. BED values are computed for $\alpha/\beta = 10$. Slater et al. [104] administered 74 Gy(BED) in 45 fractions by proton beams to 29 SCCs or lymphoepithelioma of the oropharynx and reported an 88% 5 year local control with three late GIII complications. Local control results *vs* stage were 4/4, 8/9, 9/10 and 6/6 for T stages 1, 2, 3 and 4, respectively. That is, the local control was achieved in 15 of 16 patients with stages 3 and 4 tumors. Mizoe et al. [105] irradiated 15 patients for their locally advanced head/neck squamous cell carcinoma by ^{12}C ion radiation to 70 Gy(BED) in 16 fractions. Their 5 year local control rate was 56% and no GIII late reactions. In neither series was concurrent chemotherapy part of the treatment. Again the higher dose group had the highest TCPs. Relevant to these reports is the evidence for the presence of hypoxic foci in SCC in the head and neck [41–43].

Pommier et al. [106] obtained a 3 year local control rate of 93% in 23 patients treated by protons to) 70 Gy(BED) for adenocystic carcinoma with involvement of the base of skull region. Surgery had been gross resection with positive margins in 1 patient, partial resection in 9 patients and biopsy only in 11 patients. There have been three Grade III and one IV late toxicities [17% Grade $\geqslant$III late reactions]. Mizoe et al. [105] reported a ^{12}C ion 5 year local control result of 79% in 90 patients irradiated for adenocystic carcinomas to 70 Gy(BED) in 16 fractions in 4–6 weeks]. There were no GIII toxicities. Schulz-Ertner et al. [107,108] treated 29 patients for adenocystic carcinoma to 72 Gy(BED) by stereotactic radiosurgery [SRT] + ^{12}C and 34 patients to 66 Gy SRT alone. The SRT was 54 Gy at 1.8 Gy/fraction followed by a ^{12}C boost of 3 Gy(RBE) $\times$ 6 or a SRT boost of 7 $\times$ 1.8 Gy. The 4 year local control results were 78% and 25% for SRT plus ^{12}C or SRT alone. There were two serious acute complications in each treatment group. From these series, the local control rates of the SCC and ACC were higher by ^{1}H than ^{12}C ion therapy at similar BEDs.

Mizoe et al. also reported local control of 8 of 8 locally advanced salivary gland carcinomas, four of which were adenocystic carcinomas (Dose varied between 48.6 Gy(RBE) at 2.7 Gy(RBE)/fraction and 64 Gy(RBE) at 4 Gy(RBE)/fraction. The neutron dose in the Douglas et al. paper was 18–20 Gy at ~16 fractions [110]) [109]. In the 1999 review from the University of Washington by Douglas et al. [110], the 5 year local control of salivary gland tumors in 120 patients treated by fast neutrons for gross disease was 59%. The results for tumors $\leqslant$4 cm *vs* >4 cm were 80% and 35%, respectively (read from their Fig. 2).

An impressive result from ^{12}C ion therapy by Yanagi et al. [111] is a 5 year local control rate of 84% in 72 patients with head/neck mucosal malignant melanoma by 52.8–64 Gy(RBE) in 16 fractions in 4 weeks. As noted earlier, there were good local control rates of malignant melanoma by neutron therapy [53].

Non-small cell lung cancer [NSCLC]

Local control of Stage I peripheral NSCLC have tended to be high for current high dose treatment by X-ray, ^{1}H and ^{12}C ions therapy. The patients were with few exceptions medically inoperable or had declined surgery. Results are presented in Table 5. BED values are computed for $\alpha/\beta = 10$.

Bush et al. [112] administered ~72 Gy(BED) by ^{1}H beams in 10 fractions in 2 weeks to 68 T1,2 patients. Local control results at 3 years for T1 and T2 patients were 87% and 42%, respectively. There were no GIII toxicities. Nihei et al. [113] treated 37 patients

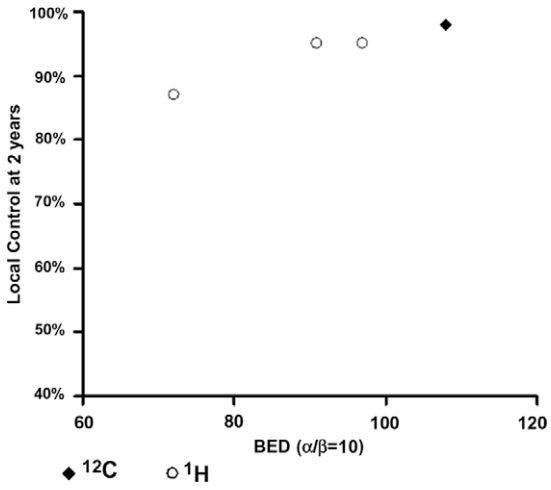

Fig. 13. Local control at 2 years for ^{1}H and ^{12}C ion irradiation of stage T1 NSCLC *vs* BED, $\alpha/\beta = 10$.

for Stage IA and B disease by ^{1}H beams employing 20 fractions in 4–5 weeks to total dose of 97 Gy(BED), *i.e.* some quite aggressive treatments. Local control was reported at 2 years as 17/17 and 18/20 for stages 1A and 1B, respectively. GIII pulmonary toxicity occurred in three patients or 8%. Hata et al. [114] treated 21 Stage 1 patients by protons to 91 Gy(BED) in 10 fractions in 15 days and obtained a 2 year local control rate of 95% with no GIII toxicities.

Miyamoto et al. [115] reported a clearly positive experience in the ^{12}C ion irradiation of 29 stage 1A and 21 stage 1B NSCLC patients to 108 Gy(BED) in nine fractions in 3 weeks. The minimum follow-up was 5 years or until death. There was I in-field and I margin failure. The actuarial 2 and 5 year local control rates were 98% (read from their Fig. 2) and 95%. Serious toxicity was a single late GIII complication, *viz.* skin damage, *viz.* ~2% of treated patients. For these NSCLC series, the TCPs were quite high, *viz.* 95–98% at 2 years following the very high doses for both the ^{12}C ion and ^{1}H treatments, *viz.* 91–108 Gy(BED). The plot of these data for 3 ^{1}H and 1 ^{12}C ion series in Fig. 13 show relative flat curve of TCP rising from 87% to 98% over the large dose range from 72 to 108 Gy(BED).

Stereotactic X-radiation therapy [SRT] is being extensively employed in high dose hypofractionated treatment of medically inoperable Stage I NSCLC patients and achieving high 2–3 year local control rates. Fakiris et al. [116] used 60–66 Gy [80% isodose volume] in 3 fractions over 1–2 weeks as treatment of 70 patients. Their 3 year local control rate was 88%. Toxicity at $\geqslant$GIII level occurred in 10% of patients with peripheral lesions but 27% with central lesions. Further there were five deaths attributed to the irradiation [116,117]. Ng [118] treated 20 patients with T1 and T2 lesions by 54 Gy [X-rays] at 18 Gy/fraction. Their 2.6 year local control rate was 90%. Hoyer et al. [119] delivered 45 Gy in three fractions of 15 Gy to 40 patients with T1,2 lesions and have reported an 85% local control result. Koto et al. [120] also employed 45 Gy three dose fractions to 31 T1, two lesions. However, the local control result at 3 years was 78% and 40% for the T1 and T2 carcinomas, respectively.

In summary, several reports document comparable 5 year local control of early stage NSCLC of 95% by very high dose ^{1}H and ^{12}C therapy. For the stereotactic radiation therapy as reported, toxicity appears to be a more significant problem.

There are reports of special categories of late morbidity in the stereotactic X-radiation treated patients. Following irradiation of 37 apical lesions, Forquer et al. [121] reported GII, GIII and GIV brachial plexopathy developed in 4, 2 and 1 patients, respectively. The actuarial 2 year risk of brachial plexopathy was estimated by at 8%

for dose to the brachial plexus of less than 26 Gy but 46% for higher doses. Another class of high risk complication is fracture of ribs. Pettersson et al. [122] estimated that the risks of rib fractures were 5% at 3 × 9.1 Gy but 50% at 3 × 16.6 in their series of 33 patients who had complete records and imaging studies at >15 months.

These results document that high 2–5 year local control rates of Stage I NSCLC are being achieved by several methods. The ^{12}C ion therapy 5 year local control result was of 95% and no GIII lung morbidity but one patient with GIII skin damage. The 2 year ^{1}H TCPs are similar to those by SRT but evidently with lesser risk of complications. The functional status at 10 or more years will provide a more secure basis for assessing the clinical efficacy of these three modalities.

Hepatocellular carcinoma [HCC]

The management of these patients has had a low success rate due to limitations of the standard treatment technology combined with the high frequency of serious co-morbidities, especially hepatitis, cirrhosis and multiple tumors. This is now changing with the introduction of particle beam therapy. BEDs have been computed for $\alpha/\beta = 10$ and 15. Here the BEDs for $\alpha/\beta = 15$ are used as that value was obtained for primary HCCs.

An important paper in 2009 was that by Fukumitsu et al. [123] of Tsukuba on the ^{1}H treatment of 51 HCC patients to 84 Gy(BED) in 10 fractions. Patients were Child-Pugh class A or B and whose tumor[s] was ⩽10 cm, [88% ⩽ 5 cm], 39% of patients had multiple tumors and were ⩾2 cm distant from porta hepatitis and GI tract. The 5 year local control rate [within the treatment volume] was 88%. New tumors subsequently developed beyond the irradiated volume in 65% of patients. In a report also from Tsukuba by Chiba et al. [124] on 162 patients and 192 tumors, the median dose was 83 Gy BED (Chiba et al. gave the dose as 72 Gy and is listed here as 79.2 Gy(RBE)) in 16 fractions in 29 days and 83% were ⩽5 cm. Some patients also received transarterial embolization and percutaneous ethanol injection [no significant effect on local control, $p = 0.22$]. The 5 year actuarial local control result was 87% for all 192 tumors. Late reactions of ⩾GII developed in five patients; acute reactions appeared in 30 patients, but these resolved within 2 weeks. The mean diameter at treatment of the 13 tumors that recurred was 4.7 cm as compared to 3.5 cm in those that did not recur. Despite very high local control rates, 5 year survival was 24% reflecting serious non-neoplastic liver disease and the development of additional HCCs.

Kato et al. [125] presented 3 year local control results of 157 hepatocellular carcinomas in 157 patients [Stage II–IVA] treated by ^{12}C ions in five successive dose escalating protocols. The patients were classed as Stage II–IVA, biopsy proven, no prior radiation to the HCC, Child-Pugh A or B and no GI tissues in contact with the tumor. Dose was progressively increased from 49.5 to 79.5 Gy(RBE) in 15 to 4 fractions. Three year local control rates increased with from 81% to 96% as dose per fraction increased from 4.3 Gy(RBE) to 13.2 Gy(RBE). Their current study is 32–38.8 Gy(RBE) in two fractions delivered to 39 patients. At a 1 year local control of 97%. There had been no severe adverse effects at the time of their report.

For the hepatocellular carcinoma series, the 5 year local control rates by hypofractionated irradiation [15 to 4 fractions] were comparable for the ^{1}H and ^{12}C ion after ^{1}H doses of 83–84 Gy(BED) *vs* ^{12}C ion doses of 67–74 Gy(BED), respectively. This is well illustrated by the plot of TCP *vs* BED in Fig. 14, for $\alpha/\beta = 15$.

Local control in 23 patients at 2.4 years by 66 Gy at 2 Gy/fraction, X-irradiation was reported results by Mornex et al. [126] as 19 of 25 patients with HCC of <5 cm or two lesions less than 3 cm.

Clearly, there have been very impressive gains in local control rates at 5 years of HCC to high dose hypofractionated ^{1}H and ^{12}C ion irradiation. These outcome results can be expected to improve further when combined with 4D IGRT. Of special interest will be the long term functional status of the liver following these dose levels. At present the results of ^{1}H appear to be ∼equivalent to those of ^{12}C therapy.

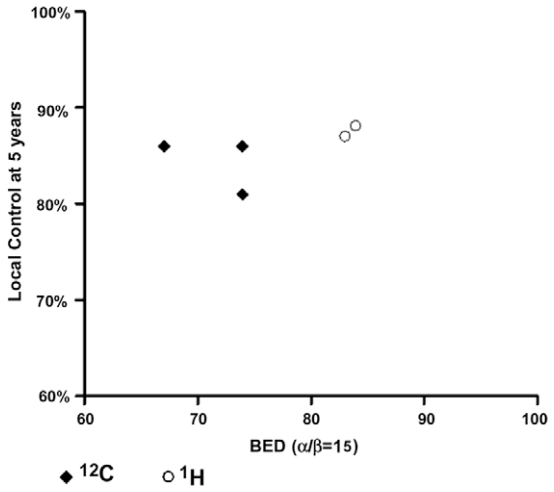

Fig. 14. Local control at 5 years for ^{1}H, ^{12}C ion irradiation of hepatocellular carcinoma *vs* BED, $\alpha/\beta = 15$.

Prostate cancer

The data on biochemical control or local control following X-ray, ^{1}H and ^{12}C ion beam therapy of prostate carcinoma are demonstrating important gains as radiation technology advances. Further, there appears to be an important advantage of combining androgen deprivation strategies for selected groups of patients.

The first Phase III clinical trial of ^{1}H *vs* X-ray [10–25 MV] beams on prostate cancer was conducted by Shipley et al. [127] from 1982 to1992 on 189 patients with stage T3–4 disease who completed the planned treatment of 50.4 Gy by X-ray to the prostate and pelvic nodes followed by an X-ray boost to 67.2 Gy or by a perineal ^{1}H boost dose to 75.6 Gy(RBE). There was no concomitant or adjuvant hormone therapy. At 5 years, local control rates were 92% and 81% (the local control rates at 8 years were 77% and 60% for the high and low dose groups, respectively) for the 75.6 Gy(RBE) and 67.2 Gy groups. Complications at 8 years in the high and low dose arms were: persistent rectal bleeding, 9% *vs* 2%; urethral stricture 4% *vs* 2% and hematuria 2% *vs* 2%.

For comparison of ^{1}H and ^{12}C ion therapy, we consider results of treatment of patients with earlier stage disease. Proton ± photon therapy was delivered to 1255 patients by Slater et al. [128] with stage I–IIIA prostate cancer who had no prior surgery or hormone therapy. Radiation dose was 74 Gy(BED) in 37 fractions. These patients did not receive hormones. The bNED (bNED is no biochemical evidence of prostate cancer) result at 5 years was 75% and the rate of GIII–IV rectal and bladder complications was ∼1%.

A Phase III trial has been completed by the MGH and Loma Linda University and reported by Zietman et al. [129] that randomly assigned patients with T1b-T2b, Mo and PSA <15 ng/ml to treatment by ^{1}H beams to the prostate to 19.8 or 28.8 Gy(RBE) followed by 50.4 Gy X-rays to the pelvis. Dose fractionation for the entire treatment was 1.8 Gy(RBE)/fraction and total doses were 70.2 or 79.2 Gy(RBE). Hormones were not employed unless a local or distant failure developed. The 5 year bNED control rates were 61% and 80% for the low and high dose groups. Late Grade III rectal and bladder toxicity developed in 2% and 1% of the 70.2 and 79.2 Gy(RBE) treated patients, respectively.

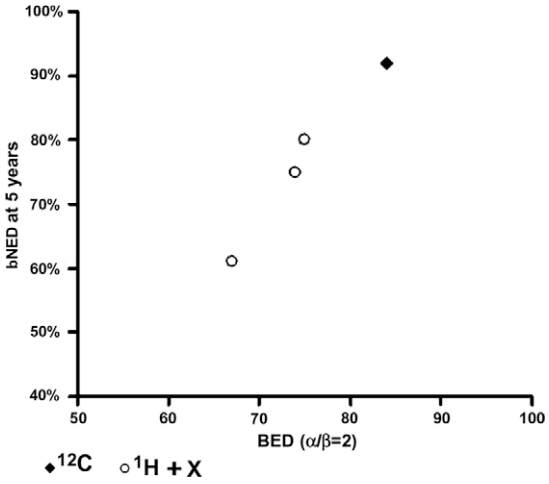

Fig. 15. bNED at ⩾5 years and BED for stage T1–2 prostate carcinoma after ^{1}H or ^{12}C ion of X-irradiation; $\alpha/\beta = 2$.

Tsujii et al. [130] reported outcome results of a series of 457 patients with stages 1–3, N0 and M0 prostate cancer treated by ^{12}C ion at Chiba. Dose levels were 80 or 88 Gy(BED) in 20 fractions. Androgen deprivation therapy was administered to intermediate risk patients for 6 months and ⩾24 months for high risk patients. The 5 year bNED rates were 92% for 295 Stage I/II and 81% for 162 Stage III patients. The 5 year bNED results are based on ASTRO definition of bNED failure. Incidence of late rectal GII and III complications were 1.8% and 0%; for bladder/urethra the rates were 5.9% and 0%.

The 92% 5 year bNED for 295 Stage T1 and T2 prostate carcinomas suggests an advantage for ^{12}C ion relative to ^{1}H and X-ray therapy. However, the ^{12}C ion dose levels were high. Probably of importance, some of the $^{12}C^{12}C$ ion but none of the ^{1}H treated patients received hormone therapy patients had hormone therapy, *i.e.* medical treatment of the ^{1}H and ^{12}C patients was not the same.

The four TCP values increased linearly with BED as illustrated in Fig. 15. IMXT at 81 Gy [1.8 Gy/fraction] by 15 MV X-rays has similarly yielded high bNED rates. Zelefsky et al. [131] treated 203, 255 and 105 patients in low, intermediate and high risk groups, respectively. Before the radiation treatment, 296 patients had a short course of hormones and that was discontinued at the completion of the irradiation. The 8 year bNED rates were 85%, 76% and 72% for the low, intermediate and high risk groups (the results are based on the ASTRO definition of bNED failure). Eight year rate of ⩾G 2 late rectal injury was 15%; for G2 and G3 bladder/urethra complications the rate 3%.

A consideration of techniques of radiation therapy employed in the prostate gland has to consider brachytherapy. With present technology this has proven to be as effective for tumor control as external beam therapy for low and intermediate risk cancers. The 5 year bNED rates for 319 favorable risk and 47 intermediate risk patients treated by ^{125}I brachytherapy was reported by 826 Zelefsky et al. [132] were 96% and 89% [132], respectively. This popular treatment method has the advantage of being a one day and relatively low cost treatment.

Renal cell carcinoma

^{12}C ions were used to deliver 72 Gy(RBE) in 16 fractions to 7 patients with stage 1 and 3 with stage 4 renal cell carcinoma by Nomiya et al. [133]. This is quite high dose treatment, *viz.* 98–117 Gy(BED), for $\alpha/\beta = 2$–5, for these assumed slowly growing tumors. Results are indeed impressive, *viz.* 5 year local control, progression free survival and overall survival rates were 100%, 100% and 74%, respectively. GII toxicity or less developed in nine patients; one patient developed GIV skin complication.

Discussion

Present status of reported results of ^{1}H and ^{12}C ion therapy

Were a gain demonstrated for ^{12}C ion therapy relative to ^{1}H therapy for the same fractionation schedule, the basis would be the higher LET and RBE for tumor than for the dose limiting normal tissues and or an improved dose distribution due principally to the more narrow penumbra.

For comparison of the TCPs and NTCPs from the conventionally fractionated ^{1}H therapy with that of hypofractionated ^{12}C ion therapy, the LQ model is employed for computation of the BED. This is a widely employed and well defined method for comparing the responses of a specified tissue to radiation administered by different fractionation schedules.

Table 8 presents the highest TCPs for ^{1}H and ^{12}C ion irradiation for eight tumor types. TCPs higher for one beam than the other by 9% points are highlighted in bold. For ^{12}C ion therapy these are skull base chordoma and prostate carcinoma while those for ^{1}H therapy are chondrosarcoma of skull base, SCC and ACC of head/neck region. The two highest TCPs by ^{12}C ion therapy for skull base chordoma were at higher doses than by ^{1}H by a wide margin. In contrast, for radiation alone of sacral chordoma, TCPs were 89% and 88% at 5 years for ^{12}C ion and ^{1}H therapy but the doses were 113 and 74 Gy(BED) respectively. For chondrosarcoma of skull, TCPs were 90% and 99% at 75 and 70 Gy(BED) for ^{12}C ions and 1H, respectively. TCPs for NSCLC were similar despite 10% higher ^{12}C ion doses, not a surprise as TCPs were at the extreme of the dose response curve. Additionally, comparable TCPs were achieved for HCC by ^{1}H and ^{12}C ion therapy, but doses were 10 and 17 Gy(BED) lower for ^{12}C ion treatment.

Table 8
Highest BED and associated TCP for ^{1}H and ^{12}C ion radiation therapy.

Tumor	α/β	^{12}C ion			^{1}H		
		BED Gy	TCP%	# Pts%	BED Gy	TCP%	# Pts
Chordoma (base of skull)	2	96	**100**	12	74	81	42
Chondosarcoma (base of skull)	2	75	90	54	70	**99**	200
Chordoma of sacrum (radiation alone)	2	113	89	36	74	88	9
SCC H/N	10	70	56	15	74	**88**[a]	16
ACC H/N	10	70	79	90	70	**93**	23
NSCLC	10	108	98	50	91, 97	95	37
HCC	10	74	86	24	84	88	51
	15	67	86	24			
Prostate	2	84	**92**	295	75	80	196

[a] The local control reported as 9 of 10 and 6 of 6 for T3 and T4 disease. The actuarial local control at 5 years was given as 88% for 12 of 13 T1 and T2 lesions combined with the T3 and T4 lesions.

Table 9
Overlap of BED and TCP.

Tumor	^{12}C ion		^{1}H	
	Gy(BED)	TCP%	Gy(BED)	TCP%
Chordoma (base of skull)	75	63	72	81
	70	60	68	59
Chondrosarcoma (base of skull)	75	90	70	99
			66	94
			66	75
SCC (H/N)	70	56	74	88
ACC (H/N)	70	79	70	93
			70	79
HCC	74	86	84	88
	67	86	83	87

Uveal melanoma TCPs were impressive at 95–98% at 2.9–15 years for X-rays, ^{1}H and ^{12}C ions for each of the five series. As doses per fraction were well above 8 Gy(RBE) per fraction, uveal melanoma is not considered further in this comparison of ^{1}H and ^{12}C ion beams.

These results indicate higher TCPs at higher dose levels. The tumor for which we have the most data are chordomas of base of skull, *viz.* 9 TCP values at 4–5 years for X, ^{1}H and ^{12}C ion irradiation [1,4 and 4 TCPs]. TCPs increased from 50 to100% with dose from 64 to 96 Gy(BED). There were seven doses in the 64–75 Gy(BED) range and one dose each at 88 and 96 Gy(BED). In comparison, for carcinoma of the prostate, the four dose levels in the range 74–84 Gy(BED) did not overlap [results given in bNED]. The doses for chondrosarcoma of skull base, SCC and ACC of the head/neck were in the range 65–75 Gy(BED).

The overlap of TCPs at similar BEDs is an important consideration. The tumors for which there is an overlap are listed in Table 9. In the dose range of 64–75 Gy(BED), ^{1}H and ^{12}C ion TCPs overlapped. Namely, for chordoma and chondrosarcoma of base of skull, SCC and ACC of head/neck region TCPs were higher for ^{1}H irradiation. For HCC, the results favored ^{12}C ion therapy in that at the much lower doses of 67 and 74 Gy(BED), the TCPs were the 86%, *viz.* the same as those by ^{1}H therapy at 83 and 84 Gy(BED). Further, the TCPs were similar for sacral chordoma at 113 Gy(BED) by ^{12}C ion therapy to 74 Gy(BED) by ^{1}H therapy. Although these results are not fully consistent with approximately equivalent TCPs at similar dose levels, dose appears to be an important determinant of TCP.

The equally important end-point of NTCP is much less straightforward in assessment for the series considered here due to the variability in end-points and scoring systems utilized. Impressive is the near consistent reporting of no GIII late tissue injury in the ^{12}C ion treated patients at Chiba. Namely, there were no GIII late injuries in the 29 chordomas of skull base, the 15 SCCs and 90 ACCs of the head/neck and 295 carcinomas of prostate. They did report 1 GIII skin injury in their series of 50 patients treated for stage 1 NSCLC [108 Gy(BED)]. At Chiba, 30 patients received ^{12}C ion therapy alone as treatment for primary sacral chordomas as described by Imai et al. [95]. The frequency of GIII and IV injury was 8 in 30 patients after doses of 113 Gy(BED). For the nine sacral chordomas treated at MGH by ^{1}H + X-radiation, there were two GIII injuries, as reported by Delaney et al. [96]. These were sacral neuropathy at 5.5 years and impotence at 3 years. At GSI, the incidence of late GIII injuries following ^{12}C ion were reported for 5% of 96 chordomas of the skull base after 75 or 96 Gy(BED), 1 of 54 patients after 75 Gy(BED) for chondrosarcoma of skull base and 2 of 29 patients treated for head/neck ACC after 72 BED Gy(BED). In contrast the incidence of GIII late injury was higher for ^{1}H irradiation of chordoma of skull base, chordoma of sacrum, carcinomas of head/neck region, stage I NSCLC and prostate.

The data reviewed here provide impressive evidence of overlaps of TCP from ^{1}H and ^{12}C ion therapy over the dose range 64–75 Gy(BED). There is a surprise in that treatment related morbidity following ^{12}C ion treatment is extremely low despite quite high BEDs. However, there has been reported a study of brain injury in 59 patients treated for head/neck tumors by ^{1}H [48] and ^{12}C ion [11] beams at Hyogo [90]. GIII brain injuries were 1 each in the ^{1}H and ^{12}C ion patients by the LENT_SOMA system and 0 in the ^{1}H and 2 in ^{12}C ion patients by the CTCAE system.

Constraints on interpretation of the available outcome data from ^{1}H and ^{12}C ion therapy

The TCPs following ^{1}H and ^{12}C ion irradiation are not dissimilar at comparable BEDs. However, on average, there is a higher associated NTCP after ^{1}H treatment. Importantly the highest TCPs for chordoma of skull base and carcinoma of prostate were by ^{12}C ion therapy with very high doses administered successfully, *viz.* minimal treatment related morbidity at this follow-up time. To the extent that this reflects an advantage of dose fractionation, dose distribution and or LET/RBE cannot be discerned from the presently available clinical outcome data because of several factors that include:

(1) No local control data from clinical trials of ^{1}H *vs* ^{12}C ion therapy. Further, the available data indicate that were there a difference, it is small.
(2) Treatments have been low dose per fraction ^{1}H and high dose per fraction ^{12}C ion therapy for most tumor types.
(3) Biomathematical models for estimating RBE values of ^{12}C ion irradiation differed between the ^{12}C ion centers.
(4) No standard protocol for scoring local failures, *viz.* in-field only, in-field + marginal, local failure as the first failure.
(5) End-points for normal tissues injury are complex and varied. The least ambiguous in the material considered here is of enucleation because of radiation injury following irradiation of uveal melanoma.
(6) TCP results need to be presented not only as a function of prescribed dose but also tumor volume and dose heterogeneity.
(7) No uniform policy in defining the margins of grossly normal tissue suspected of invasion by sub-clinical extensions of tumor to be included in the CTV. The closer the CTV conforms to the GTV, the higher the tolerated dose to the GTV and hence TCP.
(8) Doses listed for several of the studies in Tables 1–7 are mean doses.
(9) Follow-up periods have been short relative to the time required for full development of late normal tissue injury. Late injuries continue to become manifest at times remote from the radiation treatment. That is not to imply that useful information on NTCP has not been obtained from 5 and 10 year data; however they do not present the complete picture. Preston et al. [134] reported that 35% of the 442 cancer deaths attributable to the radiation from the atom bombing of Hiroshima and Nagasaki occurred between 43 and 52 years post-exposure. Further, 26% of the 250 non-cancer deaths judged to have been secondary to the radiation exposure occurred between 46–52 years after the bombing. Data on late NTCPs, *e.g.* $\geqslant$20 years will not become available for a substantial period.An inconvenient fact is that radiation treatment is whole body irradiation of a highly heterogeneous dose distribution. As mentioned earlier, the integral whole body dose for proton treatment has been calculated to be lower than that for IMXT by a factor of $\sim$2 [11]. The implication is long term survivors of radiation treated are

at risk of fatal and of less serious injury from low dose irradiation to tissues well away from the beam paths. There have been several reviews of this risk radiation treatment, see, for example, Ref. [135].

(10) Additionally, as the patients were not part of a prospective clinical trial, there were almost certainly non-trivial differences in patient/tumor characteristics, treatment planning, dose, delivery and QA between the particle beam series.

Design of clinical trials of ^{1}H vs ^{12}C ions

The need for clinical trials of ^{1}H *vs* ^{12}C is clear and pressing. The number of hospital based particle therapy centers is increasing significantly. ^{1}H centers are expected to outnumber ^{12}C centers by large factors for an extended period. Hence, the number of ^{1}H patients treated is likely to exceed the number of ^{12}C treatment patients by a factor of $\geqslant 2$. Accordingly, many more patients would be potentially available for assignment to the ^{1}H arms. Were the trial conducted by an international team that reviewed the clinical details and technical features of their treatment, the patients that met the trial criteria could be accessed and treated at their convenient ^{1}H center. For centers with ^{1}H and ^{12}C ion beams, the expectation would be that they would conduct Phase III trials and this would be as participants in the international trials. Thus, each trial would be based on matched pairing of patients treated at centers with ^{1}H or ^{12}C ion beams. The goal of the trials will be to compare TCP for treatments that yield a defined NTCP in the ^{1}H and the ^{12}C ion arms. An additional design feature could be that of assigning ^{1}H treated patients to 2–3 dose levels in each trial and thus increase the accuracy of the estimated TCP to NTCP relationship. Another factor in planning trials would be to select tumor type and stage predicted to have a TCP in the range 0.15–0.75, *viz.* the steepest portion of the dose response curve and thereby improve the likelihood of demonstrating a difference were there one. The trial design would feature identical fractionation, a standard model for selection of ^{12}C ion RBE, definition of the margin of grossly normal tissue to comprise the CTV–GTV and definition of local control.

Dose distributions by ^{1}H and ^{12}C ion beams are similar except for one major factor, *viz.* more narrow penumbras of ^{12}C ion beams. This $^{12}C^{12}C$ advantage increases with depth. The clinical reality is that in radical dose irradiation of a tumor abutting or close to a critical normal tissue[s], any reduction of penumbra provides a better conformation of the high dose volume to the PTV and lesser doses to the adjacent critical normal tissue. This positive impact of a reduced dose to a small segment of the tumor on TCP might not be large, but clearly non-zero. ^{12}C fragmentation tails are low in physical dose and BED but are not of negligible clinical concern and should be included in each treatment plan to avoid significant errors in treatment of a small fraction of patients. ^{1}H and ^{12}C ion therapy are expected to be employing progressively more narrow PT*Vs* as technology advances. With each reduction in PTV and the consequent increment in tolerated dose to the CTV and GTV, the pressure for a more narrow penumbra would be predicted to increase.

At present, CTV and GTV margins are reckoned to be the least accurate component of the treatment planning process. This is judged to be improving with the employment of new high resolution imaging techniques. The needed information is the probability of tumor cells as function of distance from the margin of the GTV determined by microscopic study of anatomic specimen. Chao et al. [136] reported the measured microscopic extensions of carcinoma of the lung and breast beyond the margins of the gross tumor in surgical specimen. There was a substantial difference in extent of sub-clinical extension between these two tumor types. This class of information should significantly improve accuracy of target definition.

An impressive finding in several of the tables is the high TCP by stereotactic high dose X-ray treatment of small tumors in one or a very few fractions. That very high dose levels to small targets yield high TCPs is no surprise, *i.e.* an increased dose increases response probability. The unanswered question is the risk of significant late NTCP. Relevant to this consideration is the reported 13% enucleation rate at less than 2.9 years following stereotactic X-ray treatment of uveal melanoma as compared with 8% at 15 years after ^{1}H therapy (Table 3).

Despite the fact that we have not encountered data demonstrating a differential RBE between human tumors and normal tissues, there is predicted an advantage of high LET irradiation of tumors that contain hypoxic cells, *viz.* a lower OER and that re-oxygenate poorly. This is expected to be a modest effect for ^{12}C ion irradiation as the OER in the mid-region of SOBP of ^{12}C beams is $\geqslant 2.2$. Additionally, there would likely be some degree of re-oxygenation that would reduce the impact of the initial hypoxic fraction. Pertinent to this point is that Phase III trials of high LET and low OER [$\sim$1.7] neutron irradiation did not yield a TCP gain for locally advanced SCCs of the head/neck region despite the presence of hypoxic cells in some of the tumors [41–43]. Additionally, the published local control results of head/neck SCCs treated by ^{12}C ions were lower than treatment by ^{1}H beams, Table 4. A highly relevant finding is that modest TCP gains have been reported from Phase III clinical trials of respiration of 0_2 at 3 ATA in fractionated X-ray treatment of SCC of the head/neck region [55]. These findings are evidence that although hypoxic cells are present in those tumors, the OERs of the neutron and ^{12}C ion beams studied were not sufficiently low to modify TCP appreciably.

Due to the higher RBE for slowly growing tumors and a lower α/β, serious consideration needs to be given to conducting of trials on one or more of the slowly growing tumors. Further, trials of tumors with hypoxic regions would be desired. ^{12}C appears to have produced very high TCPs of chordoma of the skull base [88–96 Gy(BED)], prostate [84 Gy(BED)] and renal cell carcinoma [98–117 Gy(BED). The results of apparently lower TCPs for head/neck cancers by ^{12}C ions surely merits additional study. The higher TCP by ^{1}H than ^{12}C ion irradiation of chondrosarcoma of skull base also warrants additional study.

Knowing the most effective dose fractionation protocol to be used in ^{12}C ion therapy is surely not straight forward. A clinically attractive plan to assess the gain from high LET radiations would be low RBE protons for irradiation of the CTV and PTV and high RBE ^{12}C ions for the boost dose to the GTV. The low LET dose to the CTV and PTV would be small dose per fraction to maximize the effect of fractionation on the late responding normal tissues and the high LET irradiation boost to the GTV at low dose per fraction to maximize RBE. Were the treatment to be exclusively ^{12}C ions, then the choice could be high dose per fraction for the initial component of treatment [lower RBE on normal tissues] but still small dose per fraction for the boost dose to the GTV. Limitations of cost might be less were ^{12}C ions used only as the boost dose to the GTV.

Sterotactic radiation therapy

An impressive finding in several of the tables is the high TCP by stereotactic high dose X-ray treatment of small tumors in one or a very few fractions. That very high dose levels to small targets yield high TCPs is no surprise, *i.e.* an increased dose increases response probability. The unanswered question is the risk of significant late NTCP. Relevant to this consideration is the reported 13% enucleation rate at less than 2.9 years following stereotactic X-ray treatment of uveal melanoma as compared with 8% at 15 years after ^{1}H therapy (Table 3).

Post-operative ^{12}C ion radiation treatment

We are unaware of a rationale for administering high LET in preference to low LET radiation to any normal tissues. Accordingly, high LET radiation might best be limited to patients with grossly evident tumor and that for the boost dose to the GTV. That is, high LET irradiation would not be warranted post-grossly complete resection, *i.e.* irradiation of large volumes of late responding normal tissues with small volumes of sub-clinical tumor.

Costs of particle beam therapy

The costs of ^{1}H and ^{12}C ion beam therapy are not discussed here. Our view is that our first responsibility is to develop a data base from ^{1}H *vs* ^{12}C ion clinical trials to aid assessment of the relative effectiveness of the two beams. This would provide the basis for society to decide the cost *vs* gain relationship and the priority to support clinical use of one, both or neither particle beams in radiation therapy.

The next three decades

Our expectation is that within three decades, a very large fraction of definitive radiation treatment will be based on particle beams and feature 4D image guided radiation therapy with tracking and near continuous target or beam repositioning to maintain the target correctly positioned in the beam throughout each pencil beam scanning treatment session. A responsibility for the present generation should be to determine by clinical trials if the high LET of ^{12}C ion beams is a clinical advantage and the magnitude of that advantage. Additionally, we should generate information as to clinical gain from the more narrow penumbra. Further, the role of hypofractionation in treatment plans as a function of the volume and type of normal tissue in the high dose treatment volume will need additional assessment. Hopefully, the next generation will have so advanced this specialty to consider our present high technology of treatment planning and delivery obsolete. Their interests and goals will be to move well beyond that which today is feasible to treatment strategies not yet articulated.

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