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

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ABSTRACT

Background and purpose: Relative to X-ray beams, proton [1H] and carbon ion [12C] beams provide superior distributions due primarily to their finite range. The principal differences are LET, low for 1H and high for 12C, and a narrower penumbra of 12C beams. Were 12C to yield a higher TCP for a defined NTCP than 1H therapy, would LET, fractionation or penumbra width be the basis?

Methods: Critical factors of physics, radiation biology of 1H and 12C ion beams, neutron therapy and selected reports of TCP and NTCP from 1H and 12C irradiation of nine tumor categories are reviewed.

Results: Outcome results are based on low dose per fraction 1H and high dose per fraction 12C 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 1H and 12C TCP overlaps. Frequencies of GIII NTCPs were higher after 1H than 12C treatment.

Conclusions: Assessment of the efficacy of 1H vs 12C 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 1H and 12C ion TCPs at defined BED ranges indicate that TCPs are determined in large measure by dose, BED. Late GIII NTCP was higher in 1H than 12C patients, indicating LET as a significant factor. We recommend trials of 1H vs 12C 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.

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Rationale for clinical trials of proton vs carbon ion radiation therapy

Clinical proton [1H] and carbon ion [12C] beams provide distributions of dose in Gy(RBE) (in the following text, the term dose for 1H and 12C 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 1H and 12C ion beams. Two significant dose distributional differences between these two beams are that 12C 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. 1H beams are low LET and 12C ion beams are high LET. A clear and present need is the conduct of clinical trials of 1H vs 12C ion beams with a single variable, LET. This requires that the participating 12C 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 12C 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 1H and 12C 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 1H and 12C 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, 0167-8140/$ - see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
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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.

**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.
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 \(\pm 1\%\) (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 \(^{12}\)C ions 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 communication.
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 12C ion beams are 1H 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 × 10−2 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: penumbra 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 penumbra are ~12 mm and 15 mm. In comparison, 6 MV X-ray beam penumbra at 10 cm and 25 cm depth are ~6.7 mm and 9.3 mm, a smaller increase than for the passively scattered 1H 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 penumbra. Further, the penumbra increases with thickness of the range compensator. In comparison, the penumbra of passively scattered 12C ion beams at Chiba are very narrow, i.e. ~1.5–2.3 mm between 2 cm and 15 cm depth, Ka-nai 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 of 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 1H beams for active scanning at depths up to 15 cm may differ only marginally from the 12C 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 1H beams and this advantage increases with depth. As shown in Fig. 5b the 12C 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 12C 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 1H penumbra widths on the beams from the new gantry at PSI indicated that the difference between PBS 1H and 12C 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 1H beams.
than intensity modulated X-ray therapy [24]. The lateral dose is lower for actively scanned $^1$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 RBEs 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-
pared plots of $^{12}$C ion RBE vs LET for $^{12}$C ion irradiation, ~13 keV/$\mu$m to ~80 keV/$\mu$m, for an extensive number of tumor and four normal cell lines. Fig. 7b presents the RBE 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 $\alpha/\beta$] evidenced by the increased frequency of late complications. High LET irradiation would be predicted to be more effective against slowly growing and low $\alpha/\beta$ 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.

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/$\mu$m. 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-
ishished 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 12C ion beams of LET of 13 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_{so}. 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 12C 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 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 1.2 to 7.3 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 pO2 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 pO2 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 (SF0.1) 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 12C ion beams with ranges of 14 and 24 cm. Thus, the benefit of clinical 12C 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 12C 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 RBE₂ values for cell survival and for transformation of C-H 10T¹/₂ cells irradiated by 250 kVp X-rays or by neutrons of 10 energy levels, 0.04–13.7 MeV. RBE₂ 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 1H and 12C ion therapy cannot be made on the basis of published data.

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

**Fig. 10.** RBE vs dose per fraction for late cervical spinal cord damage by 12C ion vs 15 MV X-irradiation [38].
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 $\geq$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 [1.8–2.2 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] and the fission neutron program at the MEDAP reactor in Munich. This is used for superficial lesions as 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 GSI in Darmstadt. 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 exploitation 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 α/β = 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(BED) 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 1H beam therapy at Paul Scherer Institute [PSI] near Zurich and the 12C ion beam at Gesellschaft für Schwerionenforschung [GSI] at Darmstadt. The latter has been transferred to the just opened 1H and 12C ion therapy center at the University of Heidelberg.

Doses for the different tumors are listed in Tables 1, 2 and 4–7 in Gy(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(BED).

### 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. 1H and 12C 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 1H ± X, 12C 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 1H ± X-irradiation were 54–59% for 65–68 Gy(BED) in 115, 110 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 GII complication rate was 6%, higher than in the other 11H series and the 12C 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 12C 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.**

<table>
<thead>
<tr>
<th>Beam</th>
<th># Pts</th>
<th>Dose (Gy(RBE))</th>
<th>Dose/Fx (Gy(RBE))</th>
<th>BED Gy α/β = 2</th>
<th>Local control at years</th>
<th>Late Gli Injury</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H</td>
<td>115</td>
<td>69</td>
<td>1.8</td>
<td>66</td>
<td>59% at 5</td>
<td>Not given</td>
<td>Terahara et al. [82]</td>
</tr>
<tr>
<td>1H</td>
<td>100</td>
<td>67</td>
<td>1.9</td>
<td>65</td>
<td>54% at 4</td>
<td>GI–IV: 42%</td>
<td>Noel et al. [83]</td>
</tr>
<tr>
<td>1H</td>
<td>90</td>
<td>72</td>
<td>1.8</td>
<td>68</td>
<td>59% at 5</td>
<td>GII: 6%</td>
<td>Noel et al. [84]</td>
</tr>
<tr>
<td>1H*</td>
<td>42</td>
<td>74</td>
<td>1.9</td>
<td>72</td>
<td>81% at 5</td>
<td>GII in 4/64</td>
<td>Ares et al. [86]</td>
</tr>
<tr>
<td>1H</td>
<td>10</td>
<td>52.8</td>
<td>3.3</td>
<td>70</td>
<td>60% at 5</td>
<td>GII none</td>
<td>Hasegawa et al. [88]</td>
</tr>
<tr>
<td>1H</td>
<td>19</td>
<td>60.8</td>
<td>3.8</td>
<td>88</td>
<td>91% at 5</td>
<td></td>
<td>Schulz-Ertner et al. [89]</td>
</tr>
<tr>
<td>1C</td>
<td>12</td>
<td>70</td>
<td>3.5</td>
<td>96</td>
<td>100% at 5</td>
<td></td>
<td>Debus et al. [87]</td>
</tr>
<tr>
<td>X</td>
<td>37</td>
<td>67</td>
<td>1.8</td>
<td>64</td>
<td>50% at 5</td>
<td>Serious in 1/3%</td>
<td>Martin et al. [91]</td>
</tr>
<tr>
<td>X</td>
<td>18</td>
<td>16 at Margin</td>
<td>1 Fx</td>
<td>53% at 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>33 at Max</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* This series treated by active scanning pencil beam technique.

*b* Seven fractions per week.

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

<table>
<thead>
<tr>
<th>Beam</th>
<th># Pts</th>
<th>Dose (Gy(RBE))</th>
<th>Dose/Fx (Gy(RBE))</th>
<th>BED Gy α/β = 2</th>
<th>Local control at years</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H</td>
<td>200</td>
<td>72</td>
<td>1.9</td>
<td>70</td>
<td>99% at 5</td>
<td>Rosenberg et al. [92]</td>
</tr>
<tr>
<td>1H</td>
<td>25</td>
<td>69</td>
<td>1.8</td>
<td>66</td>
<td>75% at 5</td>
<td>Hug et al. [85]</td>
</tr>
<tr>
<td>1H [PBS]</td>
<td>22</td>
<td>68</td>
<td>1.9</td>
<td>66</td>
<td>94% at 5</td>
<td>Ares et al. [86]</td>
</tr>
<tr>
<td>1C</td>
<td>54</td>
<td>60</td>
<td>3.0</td>
<td>75</td>
<td>90% at 4</td>
<td>Schulz-Ertner et al. [93]</td>
</tr>
<tr>
<td>X</td>
<td>10</td>
<td>16; 33a</td>
<td>16</td>
<td></td>
<td>80% at 5</td>
<td>Martin et al. [91]</td>
</tr>
</tbody>
</table>

*a* Median dose to margin and maximum dose.

### Table 3
**Uveal melanoma.**

<table>
<thead>
<tr>
<th>Beam</th>
<th># Patients</th>
<th>Dose (Gy(RBE))</th>
<th>Dose/Fraction (Gy(RBE))</th>
<th>Local control at years</th>
<th>Eye loss due to eye injury (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H</td>
<td>2069</td>
<td>70</td>
<td>14</td>
<td>95% at 15</td>
<td>8</td>
<td>Gragoudas et al. [97,98]</td>
</tr>
<tr>
<td>1H</td>
<td>2435</td>
<td>60</td>
<td>15</td>
<td>95% at 10</td>
<td>3b</td>
<td>Egger et al. [99,100]</td>
</tr>
<tr>
<td>1H</td>
<td>1406</td>
<td>60</td>
<td>15</td>
<td>96% at 5</td>
<td>8</td>
<td>Dendale et al. [101]</td>
</tr>
<tr>
<td>1C</td>
<td>57</td>
<td>70</td>
<td>14</td>
<td>97% at 3</td>
<td>5</td>
<td>Tsubi et al. [102]</td>
</tr>
<tr>
<td>X</td>
<td>133</td>
<td>60</td>
<td>12</td>
<td>98% at 2.9</td>
<td>13</td>
<td>Dieckmann et al. [103]</td>
</tr>
<tr>
<td>X</td>
<td>25</td>
<td>70</td>
<td>14</td>
<td>84% at 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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 1203 eyes treated in recent period of 1994–1999 3%, lower than in the earlier periods [81].

### Table 4
**Head and neck cancers.**

<table>
<thead>
<tr>
<th>Beam</th>
<th># Pts</th>
<th>Dose (Gy(RBE))</th>
<th>Dose/Fraction (Gy(RBE))</th>
<th>BED Gy α/β = 10</th>
<th>Stage</th>
<th>Local control at years</th>
<th>Late Gli Injury</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>1H + X</td>
<td>29 76</td>
<td>1.7</td>
<td>74</td>
<td>Stage I–IV</td>
<td>88% at 5</td>
<td>3 Pts</td>
<td>Slater et al. [104]</td>
</tr>
<tr>
<td></td>
<td>12C</td>
<td>15</td>
<td>57.6 or 64</td>
<td>3.6 or 4.0</td>
<td>70</td>
<td>[65–75]</td>
<td>Advanced</td>
<td>56% at 5</td>
</tr>
<tr>
<td>Adenocystic carcinoma</td>
<td>1H + X</td>
<td>23 76</td>
<td>1.6</td>
<td>70</td>
<td>Advanced</td>
<td>93% at 3</td>
<td>4 Pts</td>
<td>Pommier et al. [106]</td>
</tr>
<tr>
<td></td>
<td>1C</td>
<td>90</td>
<td>57.6–64</td>
<td>3.6 or 4.0</td>
<td>70</td>
<td>[65–75]</td>
<td>Advanced</td>
<td>79% at 5</td>
</tr>
<tr>
<td></td>
<td>1C + X</td>
<td>29 72</td>
<td>X 1.8 &amp; 30 12C 3.0</td>
<td>6.1</td>
<td>72</td>
<td>Advanced</td>
<td>78% at 4</td>
<td>2 Pts</td>
</tr>
<tr>
<td>Mucosal malignant melanoma</td>
<td>X</td>
<td>34 66</td>
<td>1.8</td>
<td>65</td>
<td>Advanced</td>
<td>25% at 4</td>
<td>2 Pts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1C</td>
<td>72</td>
<td>52.8–64</td>
<td>3.3</td>
<td>84% at 5</td>
<td>0 Pts</td>
<td>Yanagi et al. [111]</td>
<td></td>
</tr>
</tbody>
</table>
### Table 5
**Non-small cell lung cancer.**

<table>
<thead>
<tr>
<th>Beam</th>
<th># Pts</th>
<th>Dose Gy(RBE)</th>
<th>Dose/Fx Gy(RBE)</th>
<th>Stage</th>
<th>BED Gy a/b = 10</th>
<th>Local control at years</th>
<th>Late G III injury</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H</td>
<td>68</td>
<td>51 or 60</td>
<td>5.1 and 6</td>
<td>T1</td>
<td>72 [64–80]</td>
<td>87% at 3</td>
<td>None</td>
<td>Bush et al. [112]</td>
</tr>
<tr>
<td>1H</td>
<td>17</td>
<td>82 [70–94]</td>
<td>4.2</td>
<td>T2A</td>
<td>97 [79–117]</td>
<td>90% at 2</td>
<td>None</td>
<td>Nihei et al. [113]</td>
</tr>
<tr>
<td>1H</td>
<td>11</td>
<td>60a 6.6</td>
<td>T1A 91.00%</td>
<td>T2B</td>
<td>108</td>
<td>~98% at 2</td>
<td>None</td>
<td>Hata et al. [114]</td>
</tr>
<tr>
<td>1H</td>
<td>10</td>
<td>72</td>
<td>T1A 95%</td>
<td>T2B</td>
<td>108</td>
<td>88% at 3</td>
<td>None</td>
<td>Nihei et al. [115]</td>
</tr>
<tr>
<td>1H</td>
<td>50</td>
<td>72 8</td>
<td>T1A 108%</td>
<td>T2B</td>
<td>87% at 3</td>
<td>None</td>
<td>None</td>
<td>Fakiris et al. [116]</td>
</tr>
<tr>
<td>1H</td>
<td>20</td>
<td>54 [45–60]</td>
<td>T1.2</td>
<td>None</td>
<td>95% at 2</td>
<td>None</td>
<td>None</td>
<td>Ng et al. [117]</td>
</tr>
<tr>
<td>1H</td>
<td>40</td>
<td>45 15</td>
<td>T1.2</td>
<td>None</td>
<td>85% at 2</td>
<td>None</td>
<td>None</td>
<td>Hoyer et al. [118]</td>
</tr>
</tbody>
</table>

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

### Table 6
**Hepatocellular carcinoma.**

<table>
<thead>
<tr>
<th>Beam</th>
<th># Pts</th>
<th>Dose Gy(RBE)</th>
<th>Dose/Fraction Gy(RBE)</th>
<th>Size</th>
<th>BED Gy a/b = 10</th>
<th>BED Gy a/b = 15</th>
<th>Local control at years</th>
<th>Late G III injury</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H</td>
<td>51</td>
<td>66</td>
<td>6.6</td>
<td>&lt;5 cm</td>
<td>91</td>
<td>84</td>
<td>88% at 5</td>
<td>1 Lung</td>
<td>Fukumitsu et al. [123]</td>
</tr>
<tr>
<td>1H</td>
<td>162</td>
<td>72</td>
<td>4.5</td>
<td>≤5 cm</td>
<td>87</td>
<td>83</td>
<td>87% at 5</td>
<td>5 with GIII injury</td>
<td>Chiba et al. [124]</td>
</tr>
<tr>
<td>1C</td>
<td>24</td>
<td>65 [50–80]</td>
<td>4.3</td>
<td>5 cm</td>
<td>77</td>
<td>74</td>
<td>81% at 5</td>
<td></td>
<td>Kato et al. [125]</td>
</tr>
<tr>
<td>34</td>
<td>62 [54–70]</td>
<td>5.2</td>
<td>3.7 cm</td>
<td>3.1 cm</td>
<td>79</td>
<td>74</td>
<td>86% at 5</td>
<td></td>
<td>29%</td>
</tr>
<tr>
<td>24</td>
<td>53 [48–58]</td>
<td>6.6</td>
<td>3.9 cm</td>
<td>4.6</td>
<td>73</td>
<td>67</td>
<td>86% at 5</td>
<td></td>
<td>18%</td>
</tr>
<tr>
<td>38</td>
<td>50.4 [48–53]</td>
<td>12.5</td>
<td>4.6</td>
<td>3.7</td>
<td>93</td>
<td>86% at 5</td>
<td>93% at 5</td>
<td></td>
<td>28%</td>
</tr>
<tr>
<td>47</td>
<td>52.8</td>
<td>13.2</td>
<td>5 cm</td>
<td>19/25 at 2.4</td>
<td>81% at 5</td>
<td>52.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>23</td>
<td>66</td>
<td>2</td>
<td>&lt;5 cm or 2 nodules ≤3 cm</td>
<td>66</td>
<td>66</td>
<td>19/25 at 2.4</td>
<td>GIII in 4</td>
<td>Morin et al. [126]</td>
</tr>
</tbody>
</table>

### Table 7
**Prostate carcinoma.**

<table>
<thead>
<tr>
<th>Beam</th>
<th># Pts</th>
<th>Dose Gy(RBE)</th>
<th>Dose/Fraction Gy(RBE)</th>
<th>BED Gy a/b = 2</th>
<th>Stage</th>
<th>Local control or bNED years</th>
<th>Late G III injury</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>X + 1H</td>
<td>96</td>
<td>67.2</td>
<td>1.9 [1.8; 2.1]</td>
<td>66</td>
<td>T3–4, Nx, N0–2, M0</td>
<td>Local control 81% at 5 92% at 5 Urethra 2% Rectal 2% Urethra 4% Rectal 9% GIII 1%</td>
<td></td>
<td>Shipley et al. [127]</td>
</tr>
<tr>
<td>X</td>
<td>93</td>
<td>75.6</td>
<td>74</td>
<td>74</td>
<td>T1a–3</td>
<td>bNED at 5 75% bNED at 5 61% bNED at 5 80%</td>
<td></td>
<td>Slater et al. [128]</td>
</tr>
<tr>
<td>1H ± X</td>
<td>1255</td>
<td>74</td>
<td>2</td>
<td>74</td>
<td>T1b–2b</td>
<td>bNED at 5 61% bNED at 5 63% bNED at 5 70%</td>
<td></td>
<td>Zietman et al. [129]</td>
</tr>
<tr>
<td>X + 1H</td>
<td>197</td>
<td>70.2</td>
<td>1.8</td>
<td>67</td>
<td>T1b–2b</td>
<td>bNED at 5 80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>196</td>
<td>70.2</td>
<td>1.8</td>
<td>75</td>
<td>75</td>
<td>T1.2</td>
<td>bNED at 5 92%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1H</td>
<td>295</td>
<td>64.5 [63;66]</td>
<td>3.2 [3.15;3.3]</td>
<td>84</td>
<td>T1.2</td>
<td>bNED at 5 92%</td>
<td></td>
<td>Tsuji et al. [130]</td>
</tr>
<tr>
<td>X</td>
<td>203</td>
<td>81</td>
<td>1.8</td>
<td>84</td>
<td>[80;88]</td>
<td>bNED at 8 85% bNED at 8 75% bNED at 8 72%</td>
<td></td>
<td>Zelefsky et al. [131]</td>
</tr>
<tr>
<td>255</td>
<td>103</td>
<td>81</td>
<td>1.8</td>
<td>77</td>
<td></td>
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</tr>
</tbody>
</table>
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 due to superior dose distribution and or a more narrow CTV.

Local control results for $^{1}$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 chordosarcoma 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 occurrence 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. 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 $5 \times 14$ Gy(RBE) or 70 Gy(RBE). The five treatments were given on a daily basis. Results from Gragoudas et al. [97,98] for $^{4}$He 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 GII 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 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) × 6 or a SRT boost of 7 × 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 slow growing disease was 59%. The results for tumors ≤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 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 IA and IB, respectively. GII pulmonary toxicity occurred in three patients or 8%. Hata et al. [114] treated 21 Stage I 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 1 in-field and 1 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 GII 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 $^3$H and $^{12}$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 >GII 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 T1,2 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 x 9.1 Gy but 50% at 3 x 16.6 Gy 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 12C ion therapy 5 year local control result was of 95% and no GII lung morbidity but one patient with GIII skin damage. The 2 year 1H 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] on Tsukuba on the 1H 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 $\leq 10$ cm, [88% $\leq 5$ cm]. 39% of patients had multiple tumors and were $\geq 2$ 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 $\leq 5$ 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 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 12C 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 1H and 12C ion after 1H doses of 83–84 Gy(BED) vs 12C 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 1H and 12C 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 1H appear to be ~equivalent to those of 12C therapy.

Prostate cancer

The data on biochemical control or local control following X-ray, 1H and 12C 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 1H vs X-ray [10–25 MV] beams on prostate cancer was conducted by Shipley et al. [127] from 1982 to 1992 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 1H 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 1H and 12C 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–IIA 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 a biochemical evidence of prostate cancer) result at 5 years was 75% and the rate of GII–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 1H beams to the prostate to 19.8 or 28.8 Gy(BED) followed by 50.4 Gy X-rays to the pelvis. Dose fractionation for the entire treatment was 1.8 Gy(BED)/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.
Tsujii et al. [130] reported outcome results of a series of 457 patients with stages 1–3, N0 and M0 prostate cancer treated by 12C 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 carcinoma suggests an advantage for 12C ion relative to 1H and X-ray therapy. However, the 12C ion dose levels were high. Probably of importance, some of the 12C12C ion but none of the 1H treated patients received hormone therapy patients had hormone therapy, i.e. medical treatment of the 1H and 12C 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 similar TCPs for NSCLC were similar despite 10% higher BED Gy TCP% # Pts% BED Gy TCP% # Pts

<table>
<thead>
<tr>
<th>Tumor</th>
<th>12C ion</th>
<th>1H ion</th>
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</thead>
<tbody>
<tr>
<td>Chordoma (base of skull)</td>
<td>2 96</td>
<td>100 12</td>
</tr>
<tr>
<td>Chondrosarcoma (base of skull)</td>
<td>2 75</td>
<td>50 94</td>
</tr>
<tr>
<td>Chordoma of sacrum (radiation alone)</td>
<td>2 113</td>
<td>89 36</td>
</tr>
<tr>
<td>SCC H/N</td>
<td>10 70</td>
<td>56 15</td>
</tr>
<tr>
<td>ACC H/N</td>
<td>10 70</td>
<td>56 15</td>
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<tr>
<td>NSCLC</td>
<td>10 70</td>
<td>56 15</td>
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<tr>
<td>HCC</td>
<td>10 70</td>
<td>56 15</td>
</tr>
<tr>
<td>Prostate</td>
<td>2 84</td>
<td>295 75</td>
</tr>
</tbody>
</table>

We were a gain demonstrated for 12C ion therapy relative to 1H 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 1H therapy with that of hypofractionated 12C 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.

Discussion

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

Were a gain demonstrated for 12C ion therapy relative to 1H 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.
Uveal melanoma TCPs were impressive at 95–98% at 2.9–15 years for X-rays, $^1\text{H}$ and $^{12}\text{C}$ 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 $^1\text{H}$ and $^{12}\text{C}$ 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, $^1\text{H}$ and $^{12}\text{C}$ ion irradiation [1,4 and 4 TCPs]. TCPs increased from 50 to 100% 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 chordrosarcoma of skull base, SCC and ACC of head/neck region were in the range 65–75 Gy(BED).

The overlap of TCPs at similar BEDs is an important consideration. The tumor for which there is an overlap are listed in Table 9. In the dose range of 64–75 Gy(BED), $^1\text{H}$ and $^{12}\text{C}$ ion TCPs overlapped. Namely, for chordoma and chordrosarcoma of base of skull, SCC and ACC of head/neck region TCPs were higher for $^1\text{H}$ irradiation. For HCC, the results favored $^{12}\text{C}$ 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 $^1\text{H}$ therapy at 83 and 84 Gy(BED). Further, the TCPs were similar for sacral chordoma at 113 Gy(BED) by $^{12}\text{C}$ ion therapy to 74 Gy(BED) by $^1\text{H}$ 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 $^{12}\text{C}$ 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 $^{12}\text{C}$ 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 $^1\text{H}$ + 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 $^{12}\text{C}$ 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 chordrosarcoma 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 $^1\text{H}$ 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 $^1\text{H}$ and $^{12}\text{C}$ ion therapy over the dose range 64–75 Gy(BED). There is a surprise in that treatment related morbidity following $^{12}\text{C}$ 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 $^1\text{H}$ [48] and $^{12}\text{C}$ ion [11] beams at Hyogo [90]. GILL brain injuries were 1 each in the $^1\text{H}$ and $^{12}\text{C}$ ion patients by the LENT_SOMA system and 0 in the $^1\text{H}$ and 2 in $^{12}\text{C}$ ion patients by the CTCAE system.

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

The TCPs following $^1\text{H}$ and $^{12}\text{C}$ ion irradiation are not dissimilar at comparable BEDs. However, on average, there is a higher associated NTCP after $^1\text{H}$ treatment. Importantly the highest TCPs for chordoma of skull base and carcinoma of prostate were by $^{12}\text{C}$ 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 $^1\text{H}$ vs $^{12}\text{C}$ ion therapy. Further, the available data indicate that there were no differences, it is small.
2. Treatments have been low dose per fraction $^1\text{H}$ and high dose per fraction $^{12}\text{C}$ ion therapy for most tumor types.
3. Biomathematical models for estimating RBE values of $^{12}\text{C}$ ion irradiation differed between the $^{12}\text{C}$ 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. >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 ~2 [11]. The implication is long term survivors of radiation treated are

### Table 9
Overlap of BED and TCP.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>$^{12}\text{C}$ ion</th>
<th>$^1\text{H}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gy(BED) TCP%</td>
<td>Gy(BED) TCP%</td>
</tr>
<tr>
<td>Chordoma (base of skull)</td>
<td>75 63 72 81</td>
<td>70 60 68 59</td>
</tr>
<tr>
<td>Chondrosarcoma (base of skull)</td>
<td>75 90 70 99</td>
<td>66 94 66 75</td>
</tr>
<tr>
<td>SCC (H/N)</td>
<td>70 56 74 88</td>
<td></td>
</tr>
<tr>
<td>ACC (H/N)</td>
<td>70 79 70 70</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>74 86 84 88</td>
<td>67 86 83 87</td>
</tr>
</tbody>
</table>

The TCPs following $^1\text{H}$ and $^{12}\text{C}$ ion irradiation are not dissimilar at comparable BEDs. However, on average, there is a higher associated NTCP after $^1\text{H}$ treatment. Importantly the highest TCPs for chordoma of skull base and carcinoma of prostate were by $^{12}\text{C}$ 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 $^1\text{H}$ vs $^{12}\text{C}$ ion therapy. Further, the available data indicate that there were no differences, it is small.
2. Treatments have been low dose per fraction $^1\text{H}$ and high dose per fraction $^{12}\text{C}$ ion therapy for most tumor types.
3. Biomathematical models for estimating RBE values of $^{12}\text{C}$ ion irradiation differed between the $^{12}\text{C}$ 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. >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 ~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].

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 $\geq 2$. 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 convenience. 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-oxygenation 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 $\approx 2.2$. 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 ($\approx 1.7$) 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 02 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 $\alpha/\beta$ 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.

**Stereotactic 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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