NOTE

On the clinical spatial resolution achievable with protons and heavier charged particle radiotherapy beams

To cite this article: Pedro Andreo 2009 Phys. Med. Biol. 54 N205

View the article online for updates and enhancements.

Related content

- Ion beam transport in tissue-like media using MC code SHIELD-HIT
  Irena Gudowska, Nikolai Sobolevsky, Pedro Andreo et al.

- The clinical impact of uncertainties in the mean excitation energy of human tissues during proton therapy
  Abigail Besemer, Harald Paganetti and Bryan Bednarz

- Neutrons from fragmentation of light nuclei: GEANT4 study
  Igor Pshenichnov, Igor Mishustin and Walter Greiner

Recent citations

- Future cancer research priorities in the USA: a Lancet Oncology Commission
  Elizabeth M Jaffee et al

- Determination of mean ionization potential using magnetic resonance imaging for the reduction of proton beam range uncertainties: theory and application
  Atchar Sudhyadhom

- Pre-treatment patient-specific stopping power by combining list-mode proton radiography and x-ray CT
  Charles-Antoine Collins-Fekete et al
On the clinical spatial resolution achievable with protons and heavier charged particle radiotherapy beams

Pedro Andreo

Medical Radiation Physics, Stockholm University and Karolinska University Hospital, SE-171 76 Stockholm, Sweden
E-mail: pedro.andreo@ki.se

Received 2 March 2009, in final form 15 April 2009
Published 13 May 2009
Online at stacks.iop.org/PMB/54/N205

Abstract
The ‘sub-millimetre precision’ often claimed to be achievable in protons and light ion beam therapy is analysed using the Monte Carlo code SHIELD-HIT for a broad range of energies. Based on the range of possible values and uncertainties of the mean excitation energy of water and human tissues, as well as of the composition of organs and tissues, it is concluded that precision statements deserve careful reconsideration for treatment planning purposes. It is found that the range of $I$-values of water stated in ICRU reports 37, 49 and 73 (1984, 1993 and 2005) for the collision stopping power formulae, namely 67 eV, 75 eV and 80 eV, yields a spread of the depth of the Bragg peak of protons and heavier charged particles (carbon ions) of up to 5 or 6 mm, which is also found to be energy dependent due to other energy loss competing interaction mechanisms. The spread is similar in protons and in carbon ions having analogous practical range. Although accurate depth–dose distribution measurements in water can be used at the time of developing empirical dose calculation models, the energy dependence of the spread causes a substantial constraint. In the case of in vivo human tissues, where distribution measurements are not feasible, the problem poses a major limitation. In addition to the spread due to the currently accepted uncertainties of their $I$-values, a spread of the depth of the Bragg peak due to the varying compositions of soft tissues is also demonstrated, even for cases which could be considered practically identical in clinical practice. For these, the spreads found were similar to those of water or even larger, providing support to international recommendations advising that body-tissue compositions should not be given the standing of physical constants. The results show that it would be necessary to increase the margins of a clinical target volume, even in the case of a water phantom, due to an ‘intrinsic basic physics uncertainty’, adding to those margins usually considered in normal clinical practice due to anatomical or therapeutic strategy reasons. Individualized patient determination of tissue composition...
along the complete beam path, rather than CT Hounsfield numbers alone, would also probably be required even to reach ‘sub-centimetre precision’.

1. Introduction

The momentum gained by protons and other light ion therapy beams has reached considerable magnitude. Leaving aside issues on the radiobiological effects of ion therapy beams compared with those of protons and conventional electron and photon beams, which have recently been reviewed by IAEA and ICRU (2008) but still raise controversy (Wilkens and Oelfke 2008), the most common argument provided in support of all kinds of heavy charged particle beams is their pattern of energy deposition in matter. It is also acknowledged that biological studies and their comparison can only be made on the basis of uniform physical dosimetry procedures (cf Andreo et al 2000). As is well known, for these particles, the energy deposition increases along its penetration depth ending with a sharp maximum, the Bragg peak, at the end of the particle range, at the time when reduced range straggling and multiple Coulomb scattering effects result in a very narrow beam penumbra (cf Chu 1999, Kraft 2000). The recent increased interest in developing facilities world wide, notably for protons and to a lesser extent for carbon ions in several European countries, has led to multiple publications sometimes addressed to readers outside the medical physics community (cf Chalmers 2003, Brower 2009) and even to the general public in the press. In these and other publications, dose distributions from monoenergetic pencil beams of limited clinical realization are presented in comparison with those produced by broad photon and electron beams, showing how sharp and ‘precise’ dose distributions from heavy charged particles can be. Some enthusiastic defenders even claim that tumours of the size of a grain of rice, or targets as small as human cells, could be successfully irradiated with such beams.

It is well known that beams with an extended Bragg peak, produced either with range modulators or beam scanning (cf Kraft 2000), which have a less favourable peak-to-plateau dose ratio than that of monoenergetic pencil beams, are mostly used in clinical practice. However, such realistic beams are not commonly seen in many publications or manufacturers’ information. Still, when they are shown, it is commonly assumed that their range is uniquely defined and the sharp decrease in energy deposition at the distal end (the practical range of the incident particle) occurs almost exactly at a very well defined and precise depth due to the reduced range straggling. It is not unusual to refer to this type of beams as having sub-millimetre precision (Krämer et al 2000, Sommerer et al 2006), and the current spot-scanning or pencil beam-painting technical developments (cf Schippers et al 2006) are usually based on such argument.

The uncertainty in the clinical range of these particles is, on the other hand, a clinically acknowledged problem, more often discussed in the context of proton therapy (cf Goitien 2008, Lu 2008) than in heavier charged particles. It is usually related to the complexity of beam delivery and treatment planning, whenever anatomical structures and inhomogeneities modify the range, causing a ‘blurring’ of the Bragg peak. On the other hand, many investigations have been devoted to the conversion of CT Hounsfield numbers to stopping powers or water-equivalent path lengths (Schaffner and Pedroni 1998, Krämer et al 2000, Jäkel et al 2001, Minohara et al 2003, Engelsman and Kooy 2006) and even in vivo point dose measurements have been proposed for range verification (Lu 2008).

There are, however, fundamental restrictions in the accuracy of the particle range determination caused by our limited knowledge of stopping powers and its basic components, notably the mean excitation energy or I-value of a substance, as well as on projectile...
On the clinical spatial resolution achievable with protons and heavier charged particle radiotherapy beams

fragmentation and other energy loss mechanisms which compete with electronic interactions. Attention to the varying composition of similar human tissues is also neglected in most cases. It is the purpose of this work to discuss aspects of the clinical spatial resolution achievable with protons and other light ion therapy beams, and to argue that there are strong limitations on the claimed ‘sub-millimetre accuracy’ of their dose distribution for radiotherapy purposes.

In what follows, the terminology proposed jointly by the ICRU and the IAEA (Wambersie et al 2004) will be used, where the term ‘protons and heavier charged particles’ was recommended in an effort to avoid the debate between ‘light’ or ‘heavy’ ions, and the extended use of the term ‘particle therapy’ which ignores electrons, protons, neutrons and many other elementary particles used so far in radiotherapy.

2. Material and methods

For this investigation, calculations made with the Monte Carlo code SHIELD-HIT (cf Geithner et al (2006) and references therein) will be presented, a system developed for the simulation of the transport of protons and heavier charged particles in tissue-like media of interest for radiotherapy. Its most recent version 8 has been used (www.inr.ru/shield). Calculations have been made for a set of incident energies using pencil beams impinging along the longitudinal axis of a 20 cm diameter cylinder. According to the so-called reciprocity relationship (ICRU 1984a, Andreo 1988) this configuration corresponds to the calculation of the central-axis energy deposition of a broad beam.

The Monte Carlo simulations have been made in water and in a selected set of the so-called human ‘soft tissues’ whose compositions, and whenever possible their I-values, have been taken from ICRU reports 37, 44 and 46 (ICRU1984b, 1989, 1992). Whenever an ICRU recommended I-value was not available, it was calculated using the Bragg additivity rule (cf ICRU 1984b):

\[
\ln I = \frac{\sum_j w_j (Z_j/A_j) \ln I_j}{\sum_j w_j (Z_j/A_j)}
\]

where \( w_j \) is the fraction by weight and \( Z_j, A_j \) and \( I_j \) pertain to the \( j \)th constituent. Elementary I-values for the atomic constituents of materials were taken from table 2.11 of ICRU-49 (1993), identical to table 5.1 of ICRU-37 (1984b).

Even if water is the most commonly used reference material in treatment planning, there is still an ongoing debate on its I-value which affects the description of electronic energy loss by protons and heavier charged particles, basically through the well-known Bethe–Bloch collision stopping power formulae (cf ICRU 1993):

\[
(1/\rho)S_{\text{col}} = 0.307 \frac{1}{\beta^2} \frac{Z}{\bar{A}} \bar{z}^2 [L_0(\beta) + zL_1(\beta) + \bar{z}^2L_2(\beta)]
\]

where

\[
L_0(\beta) = \frac{1}{2} \ln \frac{2mc^2\beta^2W_{\text{max}}}{1 - \beta^2} - \ln I - \frac{C}{Z} - \frac{\delta}{2},
\]

\( C/Z \) being the shell correction, \( I \) the mean excitation energy, and \( L_1(\beta) \) and \( L_2(\beta) \) the Barkas (charge or \( z^2 \)) and Bloch corrections, respectively.

Both ICRU-37 and ICRU-49 recommended an I-value for water of 75.0 eV, although ICRU-49 reported with emphasis a new determination by Bichsel and Hiraoka (1992) of 80 ± 2 eV, considerably larger than the recommended 75 ± 3 eV ‘but still lying within the limits of error quoted in ICRU-37 (1984b)’. In a recent analysis, Paul et al (2007) referred to the value of
67.2 eV implicitly recommended in ICRU-73 (2005) (no uncertainty quoted). Determinations using a method similar to that of Bichsel and Hiraoka, obtained from range measurements in 70 MeV protons, can also considered to have been made by Siilver et al (1998) and Krämer et al (2000) in 195 MeV/u and 270 MeV/u carbon ions at the time of developing empirical models for depth–dose calculations, obtaining fitted values of 75 eV and 77 eV, respectively (these naturally also depend on the models used to describe interaction mechanisms other than electronic energy losses). Thus, there appears to be evidence to accept the value of 75 ± 3 eV recommended by ICRU-37 and ICRU-49, but the influence of the variation posed by the value of 67.2 eV implicitly recommended in ICRU-73 (2005) and 80 ± 2 eV by Bichsel and Hiraoka (1992) cannot be underestimated.

The default settings of the SHIELD-HIT Monte Carlo system were modified so that stopping powers for the different primaries, secondaries and higher order fragment products were computed for materials with a user-defined mean excitation energy. SHIELD-HIT does not rely on the mean excitation energy of a material (Sobolevsky 2003). Instead, the stopping power of a given medium is calculated according to the Bragg additivity rule for the stopping powers of the various constituents. In order to set a user-defined I-value for a compound, an iterative algorithm was developed where the elementary I-values of atomic constituents were allowed to vary within their ICRU estimated uncertainty until the desired I-value of the compound was reached.

The depths of the Bragg peak of protons and carbon ions were determined for each material using relevant I-values. The spread of the peak position was analysed taking into account the range of I-values mentioned above for water and the composition and estimated uncertainties of the corresponding I-values for human tissues. In order to facilitate the visualization and avoid the histogram-like distributions typical of any Monte Carlo calculation, the Bragg peaks have been fitted with the cubic spline routines in Press et al (2007).

### 3. Results and discussion

In what follows, results of the SHIELD-HIT Monte Carlo calculated depth–energy deposition are presented for protons and carbon ions of different energies impinging on water and on various human tissues.

Figures 1(a) and (b) show energy-deposition distributions in water irradiated by protons of 122 MeV, 183 MeV and 230 MeV, and carbon ions of 220 MeV/u, 350 MeV/u and 430 MeV/u. For each energy, there are three distributions corresponding to the three I-values of water used, namely 67 eV, 75 eV and 80 eV. From the onset, differences can be appreciated in these distributions, notably for the highest energies when projectile fragmentation and other energy loss mechanisms compete with electronic interactions. A comparative analysis of the overall differences in the energy-deposition patterns of the two types of projectiles is beyond the scope of this work. Instead, it is focused on the variation of the depth of the Bragg peak for a given energy and particle when the I-value of water is varied covering the range of values above.

Results are shown in figures 2(a) and (b) for 122 MeV protons and 430 MeV/u carbon ions respectively. In the case of the lowest proton energy the depth of the Bragg peaks extends over a region of 3 mm approximately; the spread extends over a region slightly larger than 6 mm in the case of the highest carbon ion energy, 430 MeV/u. The apparent ‘blurring’ of the Bragg peak position has practically identical widths for each corresponding pair of proton and carbon energies having similar practical ranges, see figure 1(a), and, clearly, an energy dependence can be observed (for the 183 MeV protons and 350 MeV/u carbon ions the spread is about 4.5 mm). This means that empirically determined water I-values obtained from proton
or carbon depth–dose distributions would appear to be different depending on the energy used for their experimental determination, pointing at the need of allowing the I-value to vary within the interval discussed above in treatment planning algorithms. This would require an increase in the margins of a clinical target volume, even in the case of a water phantom, and an ‘intrinsic basic physics uncertainty’ should be added to those margins usually considered in clinical practice.
Figure 2. Variation of the depth of the Bragg peak for the $I$-values of water 67 eV, 75 eV and 80 eV for (a) 122 MeV protons and (b) 430 MeV/u carbon ions. In the case of the proton beam the depth of the Bragg peaks extends over a region of 0.3 g cm$^{-2}$ approximately, which becomes slightly broader than 0.6 g cm$^{-2}$ in the case of the carbon ions.

The situation becomes much more complicated when human organs or tissues, rather than water, are involved in dose distribution calculations and no experimental determination is possible. Even if, as already mentioned in the introduction, considerable efforts are put into the conversion of CT Hounsfield numbers to stopping power or water-equivalent path lengths, the composition of the different body parts plays a major role in governing the interactions of protons and heavier charged particles. In this respect it is necessary to emphasize the statement...
Figure 3. Average I-values for various ‘soft tissues’, taken from ICRU reports 37, 44 and 46 (ICRU 1984b, 1989, 1992) or determined using the Bragg additivity rule for compositions adopted from the ICRU reports. Soft tissues include all tissues other than osseous tissue, teeth, hair and nails, as well as all the body fluids, etc (ICRU 1992).

(This figure is in colour only in the electronic version)

given by ICRU-44 (1989): ‘It is imperative that body-tissue compositions are not given the standing of physical constants and their reported variability is always taken into account’. Reported compositions have been obtained under different conditions for a number of human samples, and are expected to be approximated. This means that stopping power calculations and corresponding I-values are average estimates with an uncertainty considerably larger than that of water, up to the order of 10–15% (cf ICRU 1984b).

In addition, there is a large variation of I-values for similar human organs or tissues which must also be considered, although this is not usually the case in clinical treatment planning with protons and heavier charged particles. Figure 3 shows I-values for various organs and ‘soft tissues’ which, under the definition of ICRU-46 (1992), include ‘all tissues other than osseous tissue, teeth, hair and nails, as well as all the body fluids, muscle-like tissues and fatty tissues (e.g. adipose tissue)’. It can be observed that their range of variation is considerable and, for example, up to four different types of the so-called soft tissues are included whose I-values range between 70.8 eV and 74.9 eV.

Figure 4 shows energy deposition distributions of 164 MeV protons in the four soft tissues, and data for two types of muscle, skeletal and striated, have also been included. Even if all the tissues might be considered practically identical in clinical practice, differences of up to 0.3 g cm$^{-2}$ in the depth of the Bragg peak can be observed. As expected, for the case of 300 MeV/u carbon ions the variation is almost identical because of the similar practical range. It has to be noticed that these variations are exclusively due to the different compositions of otherwise assumed practically identical, or very similar, tissues.

In order to incorporate in the comparison the influence of the uncertainty of the corresponding I-values, calculations have been made for the same projectiles but considering
Figure 4. Variation of the depth of the Bragg peak for 164 MeV protons in four types of soft tissue (ICRP, ICRU-33 four-component, ICRU-44 adult female and ICRU-44 adult male), and two types of muscle (skeletal and striated), using compositions from ICRU reports 37, 44 and 46 (ICRU 1984b, 1989, 1992) and I-values from figure 3. The variation of up to 0.3 g cm$^{-2}$ in the peak position is due to the different compositions of usually assumed identical tissues.

a 10% increase and a 10% decrease of the I-values of the tissues situated at the extremes of the distributions shown in figure 4, namely skeletal muscle (increased to 82.8 eV) and female soft tissue (decreased to 63.7 eV). Results for 300 MeV/u carbon ions are shown in figure 5, where for clarity only data for these latter tissues are shown, along with the resulting distribution in water, for comparison. The change in the depth of the Bragg peak increases in this case up to nearly 0.7 g cm$^{-2}$. A similar variation is obtained for the case of 164 MeV protons.

The results shown in the last two figures demonstrate that when different human organs or tissues are to be considered, as is the case in clinical treatment planning, the need for increasing the margins of a clinical target volume, due to the combined effects of tissue composition and to the basic physics uncertainty, becomes a matter of importance in proton and heavier charged particle therapy. Again, these should be added to those margins usually considered in clinical practice, making the argument of sub-millimetre precision an issue which deserves careful reconsideration.

At this stage it could be argued that the current PET developments in protons, and especially in carbon and other ion beam treatments (cf Priegnitz et al (2008) and references therein), will allow a more accurate determination of the position of the Bragg peak in the patient. However, caution arguments against can also be raised. On the one hand, the resolution of PET devices is still far from resolving distances like the demonstrated variation of the depth of the Bragg peak, shown in the above figures. On the other hand, positron emitters are not produced in the Bragg peak, but at shallower depths. The localization of the beta$^+$ activity induced by protons and heavier charged particles relies on reconstruction algorithms that need to be developed on the basis of the uncertainty of the particle range discussed throughout this work, due to basic physics uncertainty and tissue composition.
4. Conclusions

A range of values of the mean excitation energy of water, or its $I$-value, entering into the well-known Bethe–Bloch collision stopping power formulae, have been recommended by ICRU reports 37, 49 and 73 (1984b, 1993, 2005) respectively. Specific reference was made by ICRU-49 to another value of interest, yielding a triplet of 67 eV, 75 eV and 80 eV $I$-values for water whose extremes are outside the margin provided by the recommended estimated uncertainties. The influence of this variation on the depth of the Bragg peak of proton and heavier charged particles (carbon ions) has been analysed using the Monte Carlo code SHIELD-HIT for a broad range of energies, finding a spread of up to 5 or 6 mm which is also found to be energy dependent.

The spread of the Bragg peak depth in water prompted an analysis on human tissues, which in addition to the spread due to the currently accepted estimated uncertainties of their $I$-values, also showed a spread due to the varying compositions of soft tissues provided by ICRU reports 37, 44 and 46 (ICRU 1984b, 1989, 1992). In these cases the spreads found were similar to those of water or even larger, providing support to the recommendation of ICRU-44 (1989) that body-tissue compositions should not be given the standing of physical constants.

In the light of the results shown in this work, the ‘sub-millimetre precision’ achievable in light ion beam therapy is an issue which deserves careful reconsideration. Uncertainties in stopping powers, including those of the $I$-values for different tissues (5–15%) due to their actual composition, must be taken into account to re-estimate what ‘precision’ is really achievable in clinical practice. This would require an increase in the margins of a clinical target.
volume, even in the case of a water phantom, i.e. an intrinsic basic physics uncertainty which should be added to those margins usually considered in clinical practice due to anatomical or therapeutic strategy reasons. Individualized patient determination of tissue composition along the complete beam path (and its cross section), rather than CT Hounsfield numbers alone, is probably also required even to reach ‘sub-centimetre precision’.

Acknowledgment

The support provided by Professor N Sobolevsky with the internal details of SHIELD 8 and to run the code efficiently is gratefully acknowledged.

References

Brower V 2009 European boost for particle therapy Nature 457 139
Chalmers M 2003 How particle physics can be therapeutic Phys. World 16 32–3
ICRU 1984a Radiation Dosimetry: Electron Beams with Energies between 1 and 50 ICRU Report 35 (Bethesda, MD: International Commission on Radiation Units and Measurements)
ICRU 1989 Tissue Substitutes in Radiation Dosimetry and Measurement ICRU Report 44 (Bethesda, MD: International Commission on Radiation Units and Measurements)
ICRU 1993 Stopping Powers and Ranges for Protons and Alpha Particles ICRU Report 49 (Bethesda, MD: International Commission on Radiation Units and Measurements)
ICRU 2005 Stopping of Ions Heavier than Helium ICRU Report 73 (Bethesda, MD: International Commission on Radiation Units and Measurements)
Kraft G 2000 Tumor therapy with heavy charged particles Prog. Part. Nucl. Phys. 45 S473–544
On the clinical spatial resolution achievable with protons and heavier charged particle radiotherapy beams

Priegnitz M, Möckel D, Parodi K, Sommerer F, Fiedler F and Enghardt W 2008 In-beam PET measurement of $^7\text{Li}^{3+}$ irradiation induced beta$^+$ activity Phys. Med. Biol. 53 4443–53


Sobolevsky N 2003 Private communication


Wambiersie A, DeLuca P M, Andreo P and Hendry J H 2004 ‘Light’ or ‘heavy’ ions: a debate of terminology Radiat. Oncol. 73 (Suppl. 2) iii