The Nuclear Option: Advanced Radiotherapy Techniques for Cancer Treatment

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Conventional radiotherapy techniques for the treatment of malignant tumours are known to carry some risk as a method of combatting cancerous cells. The damage caused to healthy tissue as a part of these treatments poses a significant obstacle to overcome in the fields of radiobiology and oncology. The use of linear particle accelerators and cyclotrons to generate beams of charged radioactive particles for use in cancer therapy has been developed over recent years, and new and more effective cancer treatments such as hadron therapy have been made possible because of experimental particle physics and hold the promise of greater survival rates for patients. The effectivity of such particle physics based treatments is discussed here, and potential new treatments explored.

Introduction

Standard radiotherapy is carried out in hospitals as a means of combatting cancerous cells. This treatment consists of using ionising radiation to damage the DNA of the targeted cells, rendering the cells unable to reproduce. The radiation ionises molecules in the cells, creating free radical compounds that attack and damage DNA. In order to replicate itself, the cell must repair the damage done to the DNA. Many tumours and cancerous cells possess a greatly reduced ability to repair their damaged DNA compared to normal, healthy cells. This then allows for an enhanced tumour control method, such as chemotherapy or surgery to destroy the tumour (Warrell *et al*., 1983).

The dose of irradiation is defined as the amount of energy absorbed by biological tissue. This value has been standardised in the form of the Gray (Gy), a unit defined as the absorption of 1 joule of energy by 1 kilogram of matter. The effective dose of radiation is similar to the absorbed dose, however is corrected for factors such as radiation type, tissue susceptibility to radiation, and non-uniform dosage. The effective dose is measured in Sieverts (Sv), and has the same dimensions as Gy.

Typical therapeutic doses are in the order of 20 Gy to 60 Gy over the course of several weeks (Warrell *et al*., 1983), but can be higher for tumours that are resistant to radiation damage, such as epithelial tumours like skin and oesophageal cancers (Warrell *et al*., 1983).

Radiation is highly effective in killing tumour cells, but this effectivity can, and often does, come at the cost of damage to the surrounding tissue. Tissues comprised of fast-dividing cells, such as skin, mucosal linings, and bone marrow, are extremely susceptible to the damaging effects of radiation. Diarrhoea, nausea, and vomiting are common side effects in patients who receive radiation therapy to any organs in proximity to the gastrointestinal tract (Warrell *et al*., 1983). In the case of whole-body irradiation, the lymphocytes in the blood can be damaged as much as the intended cancerous cells, and the immune system can be suppressed, leading to dangerous secondary infections (Warrell *et al*., 1983).

The most common form radiotherapy involves the bombardment of the tumour with high energy photons, typically in the MeV range. These photons are usually either X-rays created *in situ*, or gamma rays (γ-rays) from a radioactive isotope source (most commonly ^{60}Co).

The problem with these methods of administering radiation is that they don't deliver their dose to just the cancer cells. Damage to surrounding cells can be quite significant. Over the years, there have been some inventive engineering solutions to this problem, most of which involve a rotating radiation source; this allows for the largest dose to be delivered at the point of intersection of the different beam directions, thus minimising surrounding tissue damage (Warrell *et al*., 1983).

Hadron Therapy

The alternative to more common radiation therapies being developed by particle physics laboratories around the world is known as hadron therapy. Hadron therapy is the use of subatomic particles composed of quarks to treat tumours.

Most hadron therapies exhibit distinctly different energy distributions through matter than photon radiotherapy. They possess a feature, known as a Bragg peak, made evident by plotting their dose against distance into tissue, known as a Bragg curve (Figure 1). Bragg curves can be used to show where the highest dose of radiation will be delivered, and are thus used in radiotherapy to assist in calculating

the desired position and exact energy of the radiation being administered (Figure 1). The curves are named after Sir William Henry Bragg, who along with his son William Lawrence Bragg, studied such data curves during their development of X-ray spectroscopy in the early 20th century.

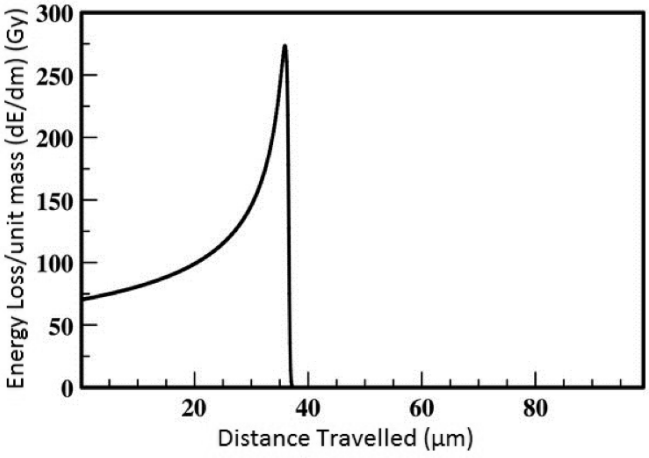

Figure 1. *A typical particle Bragg curve showing the loss of energy (dE/dx), or dose, as a function of distance travelled in water (adapted from Bevelacqua, 2015).*

The peak in the Bragg curve comes about due to Coulombic interactions between the ion particle beam and the atoms in the matter being penetrated. As the ions interact, the particles in the incoming beam have their velocities decreased by the interacting electric forces. This loss in kinetic energy is converted directly into a photon (eq. (1)), giving rise to its radioactivity. This is known as *bremsstrahlung*, or breaking radiation. The lost kinetic energy is converted directly into photons:

$$m(v_2 - v_1) = E_2 - E_1 = hf \qquad (1)$$

As the particles slow down, their interaction cross section, and thus the probability that they will have further interactions with the surrounding matter, increases (eq. (2)). The relationship between the differential cross section of an interaction, and the kinetic energy of the incoming particle can be derived to be (Rutherford, (1911)):

$$\frac{d\sigma}{d\Omega} = \frac{1}{T^2}\left(\frac{Z_1 Z_2 e^2}{16\pi\varepsilon_0}\right)^2 \left(\frac{1}{\sin\left(\frac{\Theta}{2}\right)}\right)^4 \quad (2)$$

Where $d\sigma/d\Omega$ is the differential cross section of interaction, T is the kinetic energy, given by $T = \frac{1}{2}mv^2$ for non-relativistic particles where m is the mass of the particle and v is its velocity, Z is the atomic number of the particles involved, e is the electron charge (1.6022×10^{-19} C), ε_0 is the permittivity of free space (8.85×10^{-12} F/m), and Θ is the angle of deflection.

Note the inverse relation of the cross section to the square of the kinetic energy (eq. (2)); this gives rise to the characteristic shape of the Bragg curve.

As the differential cross-section increases with decreased velocity, the incoming particles lose further kinetic energy as radiation, which leads to an exponential increase in energy lost to the surrounding tissue (eq. (2)). This exponential increase in interactions and energy losses gives the Bragg peak its characteristic exponential shape. Eventually, the particle will lose all of its kinetic energy, and this gives rise to the sharp cut-off point present on the Bragg curve of many hadrons (Figure 1).

The idea of using hadrons such as fast moving protons was first suggested just after the Second World War (Wilson, 1946). The most common form of Hadron Therapy is the use of accelerated proton beams directed at the tumour site to irradiate. Theoretically, the use of proton beams would allow for a maximum dose of radiation to be delivered at a specific point within the patient, and cause little to no permanent damage to surrounding tissue. This can be seen in Figure 2, showing the greatly reduced radiation exposure of surrounding healthy tissue after proton therapy. Such a treatment method adds additional controllability to treatment as penetration depth, position and dose targeting can all be easily manipulated in comparison to conventional photon radiotherapy (MacReady, 2012).

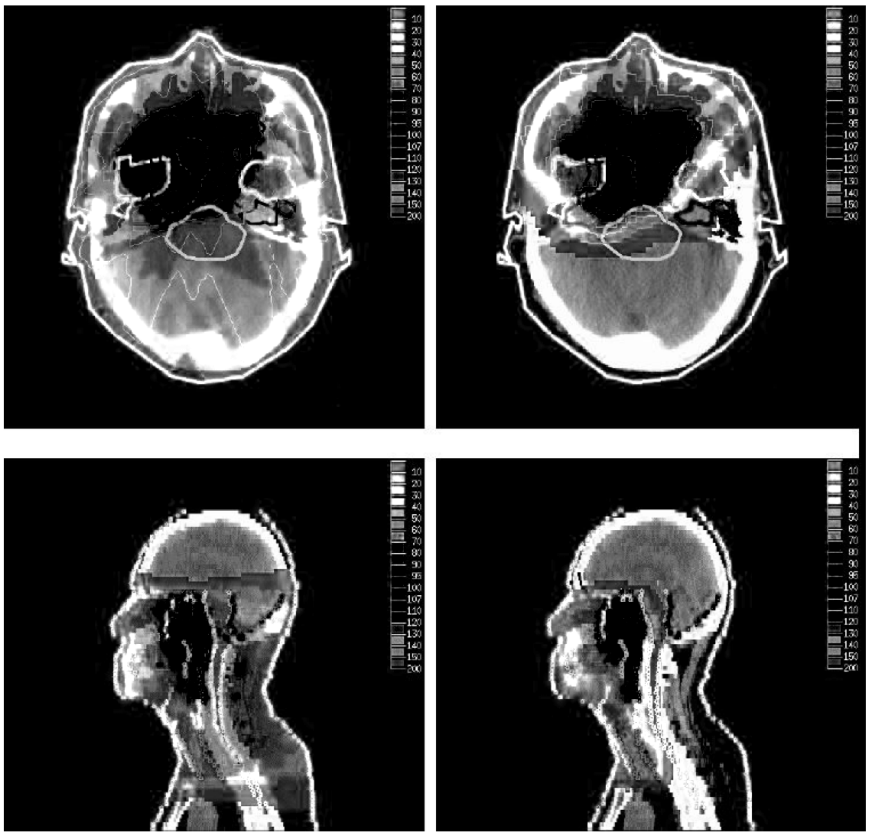

Figure 2. *Dose distribution comparison of conventional photon therapy (left) versus proton therapy (right) to treat nasopharyngeal carcinoma. The proton therapy clearly shows greater targeting of the cancerous cells, with less radiation exposure to surrounding tissue when compared to conventional photon therapy (Taheri-Kadkhoda et al., 2008).*

Proton beam therapy is already in use in cancer treatment centres across the world (*Where to get Proton Therapy*, 2014), however the facilities where such procedures are carried out are rare; only 54 such treatment centres capable of providing proton therapy exist worldwide, some of which have yet to begin treating patients (*Where to get Proton Therapy*, 2014).

This idea of using ion beams for cancer treatment is promising. There are, however, more effective ways in which the physics can be manipulated to augment treatment effectivity and lower the risk of excess damage further still. One such method is to increase the amount of energy available to be lost as *bremsstrahlung*. This can be

achieved by increasing the initial kinetic energy of protons. However, this would increase the penetration depth, and the target may be missed. A solution to this issue is offered by heavy ion beam therapy (Schlaff *et al*., 2014). This is the use of heavier ions (usually carbon) in place of protons. Increasing the mass of the ions leads to an increase in the kinetic energy when these are accelerated to similar velocities as the protons, thus leading to an increase in the amount of energy available to transfer to surrounding tissue.

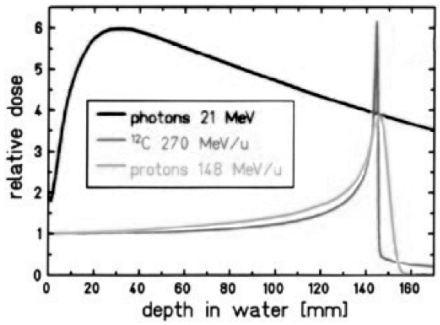

Figure 3. *Comparison of proton and C-ion beam Bragg curves to conventional photon therapy (adapted from Fokas et al., 2009).*

Carbon ions have similar characteristic Bragg curves to protons, exhibiting a much larger peak (up to 60% larger) just before coming to rest (Figure 3). A small 'tail' present in carbon ion curves can be noted. This is known as the fragmentation tail (Figure 4) (Suit *et al*., 2010). This is due to collisions of the carbon ions and target nuclei breaking into smaller radioactive particles, and contributing to the total dose (Amaldi *et al*., 2005).

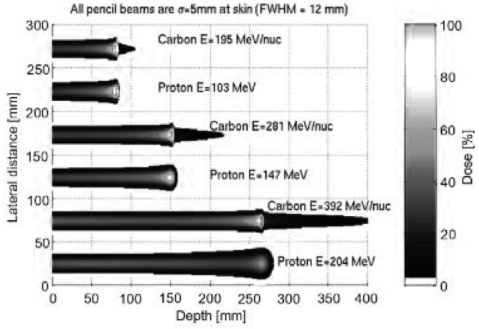

Figure 4. *Dose distribution comparison of proton and carbon ion beams. Note the fragmentation tail, and increased dose at peak for the carbon beams (Suit et al., 2010).*

There are a number of more exotic treatments under development in medical particle accelerator facilities. Hadrons consist of two main groups, baryons and mesons. Baryons are composed of three quarks (although theories suggest that exotic baryons consisting of up to nine quarks could exist, (Aaij *et al*., 2015) and make up most of the baryonic matter in the universe. Mesons are composed of one quark and one antiquark. The use of mesons for radiotherapy has similar advantages to the baryonic therapies discussed above. π-meson (or pion) beam therapy has been suggested as an alternative (Raju, 1971; Mokhovy *et al*., 1999) but is not a common treatment for cancer. The pions decay producing a number of secondary particles that in turn decay, releasing a much higher dose of radiation than from just the initial decay. Depending on the type of pion beam used in treatment, a number of decay routes are possible.

The simplest decay is that of neutral pions (π^0) into two photons (Khan, 2012). π^0 are composed of either an up and an antiup quark, or a down and an antidown quark. They thus have extremely short lifetimes (approximately 0.1 fs (Von Dardel *et al*., 1963)). However, this can prove problematic as a treatment, as there is currently no way of directly controlling a π^0 beam in a magnetic field due to its lack of electronic charge.

The more viable option, and also more complex, is charged pion decay. Charged pions have much longer lifetimes (approximately 26 ns (Perkins, 2003)) and can be easily accelerated, due to their charge. The primary mode of pion decay is a purely leptonic decay into a muon, and a muon antineutrino via a *W*-boson (Figure 5). Such particles can also decay into electrons and electron antineutrinos, or positrons and electron neutrinos, depending on the charge conservation. This decay is, however, far less probable.

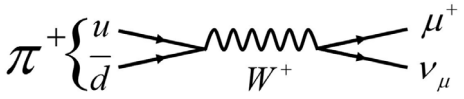

Figure 5. *Lowest order Feynman diagram showing the decay of the π^+-meson into muons and neutrinos via a W^+ boson. The decay for the π^--meson is similar, only with opposite charge conservation.*

Both the positive and negative pions can decay via this route, however the π^- has the additional option of binding to a nucleus in the tumour tissue, and interacting to the nucleus that captured it (Khan, 2012). If the nucleus in question is hydrogen, the π^- can interact with the proton, and produce a π^0 and a neutron, or a neutron and a photon (Mokhovy *et al*., 1999), as shown in eqs. (3, 4).

$$\pi^- + p \rightarrow \pi^0 + n \rightarrow n + 2\gamma \quad (3)$$

$$\pi^- + p \rightarrow n + y \quad (4)$$

The elementary muons produced in pion decay can also contribute to the total radiation dose. As the muons decay, the binding energy of the muon is released as radiation.

Figure 6. *Lowest order Feynman diagram of positive muon (μ^+) decay into a muon antineutrino, a positron and an electron neutrino via a W^+ boson.*

The exact dynamics of this decay change depending on what flavour of muon decays (Figure 6) (eqs. (5, 6)). When a μ^+ decays, it decays into a muon antineutrino, a positron and an electron neutrino via a W^+ boson (eq. (5)), releasing energy in the process. Further energy is released upon the subsequent positron-electron annihilation.

$$\mu^+ \rightarrow e^+ + \nu_e + \overline{\nu}_\mu + hf \quad (5)$$

However, if a μ^- is present, the μ^- can displace an electron in an atom, and bind to the nucleus, creating a form of exotic matter known as a muonic atom. The captured μ^- can then relax to the ground state from its excited state, releasing photons before decaying into a muon neutrino, an electron and electron antineutrino via a W^- boson (eq. (6)), along with more photons.

$$\mu^- \rightarrow e^- + \overline{\nu}_e + \nu_\mu + hf \quad (6)$$

If the μ^- is captured by a hydrogen nucleus in the tumour, further irradiation is caused by electron capture (or inverse β-decay) and the emission of a 5.1 MeV neutron (Mokhovy *et al*., 1999).

It should be noted that muon beam therapy could also be used as a cancer treatment, however, as such particles are technically not hadrons, they are simply discussed as a side-product of other hadron therapies in this review.

The most effective treatment in radiation oncology would need to be a combination of the methods previously discussed. Antiproton radiotherapy is a method that combines the dose distribution of proton therapy with the large energy releases of the other decay methods (Bassler *et al*., 2008; Kavanagh *et al*., 2013). Protons and antiprotons share similar interaction characteristics before the Bragg peak, exhibiting similar radiobiology and differential interaction cross-section. The difference between their radioactivity occurs when antiprotons reach the Bragg peak. As the antiproton comes to rest, proton-antiproton annihilation occurs. This is a complex process, involving some clean quark-antiquark annihilation, with the formation of new pions and kaons from the rearrangement of the remaining quarks of the collision (along with the gluon interactions forming strange quarks for kaon formation). The pions that are created would then decay as described above, releasing more energy, and the subsequent muon decay would release further energy still.

The decay of additional radioactive side-products of proton-antiproton annihilation increases the effective dose at the Bragg peak by about 20-30 MeV per antiproton (on average) when compared to the proton Bragg peak (Bassler *et al*., 2008). This treatment combines the increased effectiveness of heavy ion hadron therapy at the target site without the increased dose before the Bragg peak (Holzscheiter *et al*., 2006). The fragmentation tail is still observed due to the multitude of additional radioactive shrapnel particles ejected in the annihilation.

Discussion and Conclusions

While hadron therapy has many benefits over conventional radiotherapy, it is important to note some of its disadvantages. Studies have shown that while proton therapy can give far more targeted results by way of delivering the majority of radiation at the target site, the more powerful heavy-ion and antiproton therapies have drawbacks that become more noticeable when put to practical use. The fragmentation tail caused by secondary particles begins to become a serious issue when doses are applied across the entire tumour, causing a halo of damage to surrounding healthy cells (Paganetti *et al*., 2010).

Another issue surrounding these advanced tools for combatting cancer is the cost of implementing the facilities required to carry out treatments such as hadron therapy. Expensive linear accelerators, cyclotrons and synchrotrons have to be built *in situ* in order to provide these radiotherapies, and this is an expensive endeavour that not many hospitals are capable of funding. The capability of engineering cost-effective particle accelerators could enable such potentially highly effective treatments to become a more commonplace occurrence in the future.

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References

AAJI, R. *et al*. (LHCb Collaboration) (2015) 'Observation of J/ψp resonances consistent with pentaquark states in $\Lambda^0_b \rightarrow$ J/ψ K⁻p decays', *Phys. Rev. Lett*. 115(7). 072001

AMALDI, U. KRAFT, G. (2005) 'Recent applications of Synchrotrons in cancer therapy with Carbon Ions', *Europhysics News*. 36(4). pp114-118

BALLETT, P. PASCOLI, S. (2012) 'Understanding the performance of the low energy neutrino factory: the dependence on baseline distance and stored-muon energy', *Phys. Rev. D*. 86(5). 053002

BASSLER, N. *et al*. (2008) 'Antiproton Radiotherapy', *Radiotherapy and Oncology*. 86. pp14–19

BEVELACQUA, J.J. (2015) '^{210}Po microsphere radiological design for tumor vascular disruption', *PeerJ*. 3. pp1143

FOKAS, E. KRAFT, G. AN, H. EGENHART-CABILLIC, R. (2009) 'Ion beam radiobiology and cancer: Time to update ourselves', *Biochimica et Biophysica Acta - Reviews on Cancer*. 1796(2). pp216-229

HOLZSCHEITER, M.H. *et al*. (2006) 'The biological effectiveness of antiproton irradiation', *Radiotherapy and Oncology*. 81. pp233–242

KAVANAGH, J.N. CURRELL, F.J. TIMSON, D.J. SAVAGE, K.I. RICHARD, D.J. MCMAHON, S.J. HARTLEY, O.CIRRONE, G.A.P. ROMANO, F. PRISE, K. M. BASSLER, N. HOLZSCHEITER, M. H. SCHETTINO, G. (2013) 'Antiproton induced DNA damage: proton like in flight, carbon-ion like near rest', *Scientific Reorts*. 3. pp1770.

KHAN, F.M. (2012) 'The Physics of Radiation Therapy', *Philadelphia*, PA: Lippincott Williams & Wilkins

MACREADY, N. (2012) 'The Promise of Protons in Cancer Therapy', *Journal of the National Cancer Institute*. 104(9). pp648-649

MOKHOVY, N. V. GINNEKEN, A.V. (1999) 'Muons versus Hadrons for Radiotherapy', *Proceedings of the 1999 Particle Accelerator Conference*, New York.

PAGANETTI, H. GOITEIN, M. PARODI, K. (2010) 'Spread-out antiproton beams deliver poor physical dose distributions for radiation therapy', *Radiotherapy and Oncology*. 95. pp79–86

PERKINS, D.H. (2003) 'Particle Astrophysics', *Oxford: Oxford University Press*

RAJU, M.R. (1971) 'Negative pion beams for radiotherapy', *Symposium on Pion and Proton Radioherapy, Batavia, Illinois*. 4 December 1971.

RUTHERFORD, E. (1911) 'The Scattering of α and β rays by Matter and the Structure of the Atom', *Philos. Mag.* 6(21). Pp669-688

SCHLAFF, C.D. KRAUZE, A. BELARD, A. O'CONNELL, J.J. CAMPHAUSEN, K.A. (2014) 'Bringing the heavy: carbon ion therapy in the radiobiological and clinical context', *Radiation Oncology*. 9(88).

SUIT, H. DELANEY, T. GOLDBERG, S. PAGANETTI, H. CLASIE, B. GERWECK, L. NIEMIERKO, A. HALL, E. FLANZ, J. HALLMAN, J. TROFIMOV, A. (2010) 'Proton vs carbon ion beams in the definitive radiation treatment of cancer patients', *Radiotherapy and Oncology*. 95. pp3–22

TAHERI-KADKHODA, Z. BJÖRK-ERIKSSON, T. NILL, S. WILKENS, J.J. OELFKE, U. JOHANSSON, K.A. HUBER, P.E. MÜNTER, M.W. (2008) 'Intensity-modulated radiotherapy of nasopharyngeal carcinoma: a comparative treatment planning study of photons and protons', *Radiation Oncology*. 3(4).

VON DARDEL, G. DEKKERS, D. MERMOD, R. VAN PUTTEN, J.D. VIVARGENT, M. WEBER, G. WINTER, K. (1963) 'Mean life of the neutral pion', *Physics Leters*. 4. pp51-54

WARRELL, D.A. COX, T.M. AND FIRTH, J.D. (1983) 'The Oxford Textbook of Medicine (5 ed.)', *Oxford: Oxford University Press*

WILSON, R.R. (1946) 'Radiological use of fast protons', *Radiobiology*. 47(5). pp487-491

'Where to get Proton Therapy', *http://www.proton-therapy-today.com/where-to-get-pt/*, 10th February 2016.

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