Radiation from K-shell filling in highly charged ions: a driver for resonant combination cancer therapy?

A P Kavanagh, J D Gillaspy¹, D G Hirst, M H Mendenhall², N Nakamura³, S Ohtani³, H Watanabe³ and F J Currell

Queen's University Belfast, Belfast BT7 1NN, United Kingdom
¹NIST, Gaithersburg, MD 20899-8421, USA
²Vanderbilt Univ. FEL Centre, Nashville, TN 37235-1816 USA
³Inst. for Laser Science, The Univ. of Electro-Communications, Tokyo 182-8585, Japan

Email: f.j.currell@qub.ac.uk

Abstract. The possibility of using x-radiation from bare and hydrogen-like highly charged ions as a driver for a proposed form of cancer therapy is discussed. This proposed form of therapy, called resonant combination therapy, benefits from a very high contrast ratio between dose to the tumour and dose to the surrounding healthy tissue as is illustrated by some simple model calculations of isodose/ion distributions. The need for further radiobiological measurements and ion source developments in order to make this form of therapy feasible are highlighted.

1. Introduction
Failure occurs in 30-95% of radiotherapy treatments depending on the site of the tumour [1] while critical normal structures in the vicinity of the tumour can limit the dose that can be given. Control of the primary tumour has also been shown to limit the development of metastases [2-4], so the development of techniques to enhance the effective radiation dose in tumours, while sparing normal tissues, would be of great benefit. The scheme proposed here involves impacting slow bare or hydrogen-like heavy ions onto a surface, resulting in one high energy photon (i.e. >30keV) per K-shell vacancy with the energy of these photons being dictated by the atomic number (Z) of the highly charged ion used. A particular ion is selected so that these photons lie just above the K-edge of a heavy atom species preferentially incorporated into the tumour leading to a large local dose as required. Recent measurements made using ions extracted from the Tokyo EBIT [5] confirm the expectation that one high energy photon is produced per K-shell vacancy.

2. Conceptual basis of the proposed therapy scheme
Hainfeld et al have intravenously delivered 1.9 nm gold particles to achieve a 0.7%wt/wt concentration of gold, while maintaining an order of magnitude less concentration in the normal tissue due to the trapping of the nanoparticles within the tumour vasculature [6]. This resulted in an impressive enhancement of tumour response to 250 kV x-rays, offering the potential for preferential enhancement of the effectiveness of radiotherapy.
The underlying concept for this therapy scheme can be understood from figure 1. Here linear piecewise approximations to the mass attenuation coefficients for soft tissue doped with 0.7%wt/wt and 0.07%wt/wt of iodine are illustrated. Linear piecewise approximations are used since they make the calculations described in section 3 straightforward. These traces then are reasonable approximations to the mass attenuation coefficients which might be expected for healthy and cancerous tissue, respectively, for similar uptakes of iodine to that of gold achieved by Hainfeld [6].

![Figure 1. Linear piecewise approximations to the mass attenuation coefficients of healthy and cancerous tissue and the x-ray spectrum which would arise if a mixture of 50% bare and 50% H-like cerium (Z=58) ions impacted onto a surface and the resultant x-rays were filtered by 0.25 mm of Al.](image)

S(E) was derived from the measurements of Watanabe et al [5], performing a $Z^2$ scaling on the energy axis and then using a Beer-Lambert law calculation for the filtration using standard data [7]. Cerium was chosen so that the radiation lies just above the K-edge of the iodine dopant. It is clear that the mass attenuation coefficient of the cancerous tissue is significantly enhanced across the whole of the spectrum, suggesting that exposure to this irradiation would result in a significantly greater dose to the tumour. This is the conceptual basis of the new therapy scheme proposed.

![Figure 2. Layout of the system envisaged for resonant combination therapy using highly charged ions.](image)

An example of the set up envisaged for this proposed form of radiotherapy is shown in figure 2. Ions are transported from a high performance electron beam ion source/trap (EBIST) which has been configured to produce predominantly bare and hydrogen-like heavy ions, chosen so that the K-alpha radiation from these ions lies just above the K-edge of a heavy atom dopant previously incorporated into the patient. The ions are transported through a rotatable gantry and focused onto a thin aluminum window (typ. 0.25-0.5 mm). This window acts both as an electron rich target, generating the high energy photons and also as a high-pass filter, attenuating low energy (<20 keV) x-rays. The resultant x-rays are then collimated using a multileaf collimator so as to target the tumour. Both the angle of the gantry and the patient's position can be varied to allow for multi-field irradiation, reducing the entry dose experienced by the patient.

3. Model calculations
To assess the feasibility of the proposed scheme, we have developed a simple model from which isodose distributions can be derived. Ignoring all secondary processes, the energy flux of radiation with a properly normalized spectrum $S(E)$ (see figure 1) due to ions impinging on a surface with a rate $R$ is given by:
\[
\phi = R \int S(E) E \left( \prod_i e^{-\tilde{\mu}_i(E) l_i} \right) dE \times \frac{dA}{4\pi r^2}, \quad \tilde{\mu}_i(E) = \sum_j w_j \left( \frac{\mu_j(E)}{\rho_j} \right),
\]

where \( r \) is the distance between the source and the small element of surface \( dA \) and \( \tilde{\mu}_i(E) \) is the effective mass attenuation coefficient for a medium (labeled by \( i \)) of length \( l_i \) through which the ray has passed. The product is over all media, \( i \), between the source and the small element. The effective mass attenuation coefficient \( \tilde{\mu}_i(E) \) for any medium can be calculated from \( w_j \), the partial densities of the constituents and the mass attenuation coefficients for the constituents \( \left( \frac{\mu_j(E)}{\rho_j} \right) \), readily available in tabular form [7]. The mass attenuation coefficients of figure 1 were derived in this way.

To speed up the calculations, the mass attenuation coefficient was averaged over the spectrum \( S(E) \) to give the following equation set from which the dose due to any ray can be derived:

\[
\phi = \tilde{\psi} \left( \prod_i e^{-\tilde{\mu}_i l_i} \right) \times \frac{dA}{4\pi r^2}, \quad \tilde{\psi} = R \int S(E) E dE
\]

\[
\left( \tilde{\mu}_i \right) = \sum_j w_j \int \frac{\mu_j(E)}{\rho_j} S(E) dE \quad \frac{1}{S(E) dE} \int S(E) dE \quad D = \phi \frac{\tilde{\mu}_i}{\rho_i}
\]

where \( t \) is the time for exposure to the radiation and \( \rho_i \) is the density of medium \( i \) and \( D \) is the dose at the point of interest. For a source point and a location where the dose is required, the equation set (2) is a recipe from which the contribution to the ray can be computed providing the geometry of the media comprising the system is defined.

A large number of rays are considered using equation set (2), originating from an array of source points chosen to mimic the effect of swinging the gantry around the patient. The effect of the multileaf collimator was included again by the selection of allowed rays. These rays travel to an array of destination points chosen to correspond to an interesting cross-section through the patient. By calculating the total dose at each point (effectively integrating over the therapy session), an isodose distribution can be derived on a standard PC in a few minutes. If one sets \( R=t=1 \) then the isodose distributions become isodose/ion distributions as are shown in figure 3. We have also developed more sophisticated and computationally expensive simulations making use of established Monte-Carlo transport codes [8] but these lead to essentially the same conclusions as those presented here.

4. Results of isodose/ion distributions for head and neck tumours

Figure 3a shows results from calculating the isodose/ion distribution of a neck tumour as described above (neck radius 7 cm, tumour radius 0.5 cm, centred 4 cm below the surface of the neck) doped with 0.7%wt/wt iodine. Illumination was due to 50% bare, 50% H-like Ce (Z=58) ions impacting on a surface and filtered by a 0.25 mm Al filter. The maximum dose/ion on this plot is about \( 1.8 \times 10^{-15} \) Gy/ion with doses below 10% of this level not being shown. Instead light grey is used to show unaffected tissue. The outline of the tumour is clear from the lighter regions due to the expected enhancement. Calculations for heavier dopants, illuminated by x-rays from the correspondingly heavier ions (roughly \( Z_{\text{ion}} = 1.15Z_{\text{dopant}} \)) show similar dose distributions although the contrast gets slightly worse as \( Z \) increases due to the relative reduction in the K-edge. This seems to suggest that lower \( Z \) is preferable although there is a trade-off regarding penetration. Figure 3b shows similar results for a head tumour, doped with tungsten and illuminated with x-rays from bismuth ions, filtered by 0.5 mm of Al, all other things being the same as before. The radius of the skull (shown as dark grey) was 8.5 cm, it was 1 cm thick and the tumour was centred 3 cm below the surface. The maximum dose/ion to the tumour was about \( 2 \times 10^{-15} \) Gy/ion. A similar simulation for iodine doping showed far a higher entry dose than that experienced by the tumour due to the absorption of the skull. For this tumour then, a higher \( Z \) dopant is preferable.
These isodoses/ion plots show an unprecedented contrast between the dose to healthy and cancerous tissue, suggesting that the proposed form of therapy would be extremely attractive if sufficient ions can be delivered. Typical doses are of the order of 1Gy and should be delivered on the order of 1000 seconds or less to be practical, putting a required ion delivery rate of \(10^{10}\) ions/second or even \(10^{11} - 10^{12}\) ions/second after allowing for additional geometry efficiency factors, beyond present ion source capabilities for such highly stripped ions [9]. Therefore, improved ion sources must be developed for this therapy scheme to become feasible. However, the calculations presented here have been pessimistic in a number of ways so this is an upper bound on the source requirements. The tumours considered are deep-seated and hence difficult to treat, other tumours would have an order of magnitude lower requirements in terms of ion delivery. Furthermore, the relative biological efficiency (RBE) for irradiation above the K-edge might be significantly greater than 1. Indeed there is significant radiobiological data to support this. Finally, if a greater uptake of the heavy dopant can be achieved, this also helps to reduce the requirements of the ion source. These three research themes are being pursued in parallel in order to achieve this important goal. As new radiobiological data becomes available, the ion source requirements can be properly defined.

Figure 3. Isodose plots for simulated (unoptimised) treatment of a) neck and b) head tumours.

5. Conclusion

A new form of therapy has been proposed and while the required dose delivery is above that produced by the present generation of ions sources, there are reasons to be optimistic that the required ion fluences can be delivered. Ongoing research into the underlying radiobiology and dopant delivery might significantly reduce the requirements placed on the ion source while ion source developments will raise the achievable fluences. Hopefully the requirements and the realisable ion currents will soon meet when radiation from highly charged ions can become a major tool in the oncologists armoury.

References
[1] Steel G G 2002 Introduction: the significance of radiobiology for radiotherapy (Basic Clinical Radiobiology) ed G G Steel (Arnold, London)
[2] Arriagada R, Rutqvist L E, Mattsson A et al 1995 Adequate locoregional treatment for early breast cancer may prevent secondary dissemination J Clin Oncol 13 2869–2878
[3] Fuchs Z, Leibel S A, Wallner K E et al 1991 The effect of local control on metastatic dissemination in carcinoma of the prostate: Long-term results in patients treated with 125I implantation Int J Radiat Oncol Biol Phys 21 537–547
[4] Leibel S A, Scott C B, Mohiuddin M et al 1991 The effect of local-regional control on distant metastatic dissemination in carcinoma of the head and neck: Results of an analysis from the RTOG head and neck database Int J Radiat Oncol Biol Phys 21 549–556
[5] Watanabe H et al, elsewhere in this volume
[6] Hainfeld J F, Slatkin D N, Smilowitz H M 2004 The use of gold nanoparticles to enhance radiotherapy in mice Phys Med Biol. 49(18) N309-15
[7] http://physics.nist.gov/PhysRefData/
[8] Allison J et al 2006 Geant4 Developments and Applications IEEE Trans. Nuc. Sci. 53(1) 270
[9] Gillaspy J D 2006 these proceedings