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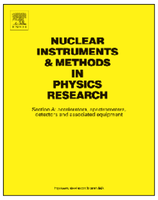

# Potential clinical impact of laser-accelerated beams in cancer ion therapy

Ceferino Obcemea

*Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, 777 N. Broadway, Suite 100, Sleepy Hollow, New York, NY 10591, United States*

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ABSTRACT

In this article, I present three advantages of plasma-accelerated ion beams for cancer therapy. I discuss how: 1. low-emittance and well-collimated beams are advantageous in proximal normal tissue-sparing; 2. highly-peaked quasi-monoenergetic beams are ideal for fast energy selection and switching in Pencil Beam Scanning (PBS) as a treatment delivery; 3. high fluence and ultra-short pulse delivery produce collective excitations in the medium and enhance the stopping power. This in turn produces denser ionization track signatures (spurs, blobs, etc.) in target tumors, higher linear energy transfer, higher Bragg peak, and higher radiobiological effectiveness at the micro-level.

## 1. Introduction

A primary concern in cancer treatment is to attack the disease with minimum morbidity. The "*primum non nocere*" ("First, do no harm") principle embedded in the Hippocratic Oath, puts a boundary on how aggressive one can be in attempting to heal the patient. All efforts must be made so that the "cure" shall not have effects more deleterious than the disease itself. For this reason, many therapeutic approaches have evolved to minimize the toxicity to normal organs and tissues. For example, surgical techniques are now evolving into more minimally-invasive surgery, systemic chemotherapy into receptor-based targeted therapy, and radiation therapy into more conformal, dose-painted IMRT techniques [1–3], all aimed at sparing normal tissue during treatment procedures.

Particle ion beams are becoming an important addition to the treatment regimens in cancer therapy. This is due to their superior energy deposition pattern compared to the traditional photon and electron beams from linear accelerators. Ion beams deliver a low entrance dose, followed by a rapid dose build-up at the desired depth/s and a sharp fall-off distal to the Bragg peak.

A couple of issues however prevent ion beams from being more widely adopted in the clinic: First, the high cost (around \$250 M) of a multi-gantry $p^+$ installation, plus maintenance costs (ca. \$10 M/yr). Second, the huge footprint required for the facility. The proton gantry alone is multi-story high, and for carbon $C^{6+}$ the size is even more staggering [4]. Third, the difficulty to accelerate multiple ion species with a single machine. Without drastic machine modifications, a cyclotron or a synchro/-cyclotron can only accelerate the ion species that it was originally designed for. Yet, it has been argued that, based on radiobiological grounds, a combination of particle beams from various ion species might be therapeutically more efficacious [5].

It has been noted that the three issues above could be solved with the technology of laser-accelerated beams [6]. Here I would argue that laser acceleration offers advantages that go beyond those three issues because it can deliver a qualitatively/clinically more effective beam. The unique advantages of laser-accelerated beams result from low-emittance, high fluence, close microbunching and ultra-short pulse delivery which I will discuss below.

## 2. Unique advantages of laser-accelerated beams

Laser-accelerated ion beams are produced from the interaction of intense ultra-short laser pulses with solid thin foils, gas plumes, or cryogenic condensate target materials. Regardless of the acceleration schemes (TNSA, RPA, BOA, etc.) at play, the resulting ion beams can be highly peaked in energy, with high current, high fluence ($10^{13}$), with low emittance (μm mrad) and bunched in ultra-short (ps) pulses [7]. Hence, each pulse consists of a large ion cluster, inside which the constituent ions have very short inter-particle distance, and each cluster gets delivered in ps wave trains. Very high acceleration gradients (10 TV/m) can be achieved in a very short distance. These metrics are orders of magnitude superior to conventional rf sources. Thus, the beam delivery of laser-accelerated ions is very compact, deliverable in a much smaller footprint, and with lower corresponding facility costs. More important than these cost-cutting aspects are the clinical consequences of the characteristics of these beams, as follows.

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### 2.1. Low-emittance

This beam characteristic gives rise to sharper penumbra of the treatment fields. The sharper the penumbra, the better one can spare tissues outside the treatment field. The smaller the volume of normal tissue getting irradiated, the lower is the toxicity (volume-effect). Using the new mini-grid technique [8] where the entering beam gets evenly split into mini-beams, one can further reduce the dose to normal tissues proximal to the tumor target. With this technique, the entrance beam is split into evenly-spaced mini-beams, sparing the tissues at the gaps. As these mini-beams penetrate the body, they begin to diverge due to multiple Coulomb scattering so that at the depth of the tumor target, they become fully interlaced and hence deliver the full dose. The intervening normal tissues proximal to the target would receive a much lower dose. Combined with the distal tissue sparing by the Bragg peak, dose to the target tumor can then be maximized with much less toxicity to all surrounding normal tissues. There is also indication that this mini-grid scheme activates a growth factor HIF-1 that facilitates vasculature repair of the irradiated normal tissues [9].

### 2.2. Highly peaked energy spectrum

Quasi-monoenergetic beams or highly-peaked energy spectrum would be ideal for fast energy selection and switching in Pencil Beam Scanning delivery (PBS). The PBS treatment delivery is now the new gold standard to enable to dose-paint the tumor target volume with precision and speed [10]. With copious number of ions in the peaked energy bin, dose-painting to a given depth/volume would be more efficient.

### 2.3. High fluence and ultra-short pulse delivery

The energy loss of a charged particle as it penetrates a medium can be described by its stopping power. The dominant mechanism is its interaction with the bound electrons of the stopping material and, for binary collisions, it is given by the well-known Bethe–Bloch (BB) equation:

$$-\frac{dE}{dx} = \frac{4\pi}{m_e\, c^2}\frac{nz^2}{\beta^2}\left(\frac{e^2}{4\pi\epsilon_0}\right)^2\left[in\left(\frac{2m_e c^2\beta^2}{I\left(1-\beta^2\right)}\right)-\beta^2\right] \tag{1}$$

However, when the incident charge is an ensemble of particles, such as in a high-fluence beam, the stopping power can be best described by the dielectric response of the target material, i.e.

$$-\frac{dE}{dx} = S_p = \frac{1}{2\pi^2 v}\int d^3k\frac{k\cdot v}{k^2}\,Im\left[-\frac{1}{\varepsilon(k, w=k\cdot v)}\right] \tag{2}$$

where $S_p$ is the proton stopping power, $\varepsilon$ is the dielectric function of the medium, $w$ is the frequency and $\nu$ is the velocity of the projectile. For a cluster of $N$ ions with atomic charge $Z_i$ and relative positions $r_{ij}$, the cluster stopping power [11] is given by:

$$S_{cl} = \left[\sum_{i=1}^{N} Z_i^2 + \sum_{i\neq j}^{N} Z_i Z_j . I\left(r_{ij,}\theta_{ij}\right)\right] S_p \tag{3}$$

with $\theta_{ij}$ as the angle of the vector $r_{ij}$ and the vicinage function $I$ integrated over $\theta_{ij}$ is given by:

$$I(r,\theta) = \frac{1}{2\pi^2\nu S_p}\int_0^\infty\frac{dk}{k}\int_0^{k\nu} dw\, w\, Im\left[-\frac{1}{\varepsilon(k,w)}\right]$$

$$\cos\left(\frac{wa}{v}\right) J_0\left[b\left(k^2-\frac{w^2}{v^2}\right)^{1/2}\right] \tag{4}$$

where $a$ and $b$ are the orthogonal components of vector $r$ and $J_0$ is the zeroth order Bessel function.

This dielectric formalism of the stopping power [12] has had a long history dating back to Fermi, Vlasov, Veksler, Lindhard and others and has been used to describe the energy deposition of ion clusters impinging on plasma, solid foils, and other condensed matter. What we have learned from these studies is that in addition to the binary collisions as described by the BB equation, there are also collective oscillations induced on the target by the impinging ions. If the ion cluster is sufficiently large and the interparticle distance between the constituent ions sufficiently small, then the collective oscillations set by the ion ahead would be felt by the next trailing one. Alternatively, if the ion clusters come in very short pulses or wave trains, the collective wakes set off by the first cluster affect as a retarding force the trailing one that follows [13]. This retardation by the collective wakes (vicinage effect) result in an increase of the stopping power and is proportional to the projectile cluster size and velocity (i.e. relative to the Fermi velocity of the target electrons) [14]. The first experimental confirmation of this collective effect was on proton clusters impinging on C and Au foils [15], with later studies [16] on other projectile clusters of $H^{2+}$, $H^{3+}$, $C^+$, $B^+$, $O_2{}^+$, and $O_3{}^+$ showing similar results of enhanced stopping power. In the context of high energy electron clusters as projectile, Tajima et al. [17] have recently invoked this collective effect to propose a tenuous plasma as a compact beam dump, obviating radio-activation as a radiological hazard in the operation of laser wakefield accelerators. Note that these collective wakes are not observable with ions from conventional sources because (a) the cluster size/fluence is low and (b) the pulse length is too long, so that by the time the next ion/cluster arrives, the collective plasmon excitations in the medium caused by the previous ion/cluster would have already died down and gone to equilibrium.

The effect of close clustering of N ions (say $p^+$) inside the projectile of charge Nz is also apparent in the BB equation above. When the clustering is very sparse with large inter-particle distance, the stopping power of the cluster ($S_{cl}$) is simply the sum of the stopping power $S_{p+}$ of individual $p^+$, i.e., $S_{cl}\propto NS_{p+.}$ However, in the limit when the clustering becomes so tight that the interparticle distance approaches that between nucleons, then $S_{cl}\propto N^2S_{p+}$. Thus the stopping power of the nucleon cluster is enhanced by a factor of N compared to a cluster of independent particles. In regular beam clusters, where the inter-particle distance is obviously greater than that between nucleons, the enhancement of $S_{cl}$ due to vicinage effects would be much less than N, but nonetheless greater than 1. The order of magnitude would depend on the number N, the degree of clustering in the projectile, the velocity of the projectile, the magnitude of collective excitations generated in the medium, and how fast their relaxation times are. For example, experiments [18] of fast hydrogen clusters impinging on $SiO_2$ showed that collective excitations (plasmons) were induced by the incident ions in the medium and the vicinage effects of these plasmons led to an enhanced stopping power of 1.2. Analytical calculations [19] using the dielectric formulation of $S_{cl}$ with the target medium modeled as a systems of spherical harmonic oscillators yield an enhancement of 1.5, in qualitative agreement with the experiment. A similar enhancement range was obtained by Arista et. al. [11] simulating large ($N$=104, 354) hydrogen clusters with the target medium model of an electron gas at finite temperature. In their calculation of Eq. (4), they found the enhancement factor to be around 1.5–1.8.

The detailed understanding of vicinage effects of ion-cluster beams in biological media is very complex, although its potential role in energy deposition of therapeutic ion beams has not been noticed before. In general, biological media are more complex because of the inhomogeneous distribution of composite, highly ordered electronic structures (e.g. extensive π-electron rings in the

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