Moderate-energy Carbon Ions for Intra-Operative Radiation Therapy: A Feasibility Study


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(Dated: January 16, 2015)

Abstract

At present, the primary medical use of carbon ion beams is the precise treatment of deep-lying tumors. The superficial irradiation of surgically resected tumor beds with beams of carbon ions at moderate energies might provide a cost-effective possibility to make use of their advantageous characteristics for a much larger number of pathologies. We sketch the outline of a compact device for the acceleration and application of these particles and study its technical feasibility. Its key component is a carbon ion source, based on laser-plasma interaction, with a maximum energy of 480 MeV (40 MeV/u). While the energy and spectral distribution of ions accelerated by laser are often considered inadequate for the treatment of deep-lying tumors, the physical requirements for the proposed application are less stringent. From a review of published data we conclude that carbon ions in the required energy range, an order of magnitude below current external beam therapy facilities, have been demonstrated in laser-plasma interactions. Further experiments are required to achieve similar results at reduced laser power. Based on realistic ion spectra various aspects of a superficial irradiation are investigated, like the depth-dose profile and the production of secondary isotopes, as well as practical details of the therapy system. GATE simulations show that continuous carbon ion spectra in the range 100-480 MeV can be superposed to provide an approximately uniform depth-dose profile for a radiation boost of 10 Gy after a surgical intervention. In order to complete the irradiation of a 30 cm$^2$ wide area within ten minutes a laser pulse rate of 10 Hz is required. Prompt gamma emitting isotopes are produced in sufficient abundance to allow for online-monitoring of the administrated radiation dose.

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I. INTRODUCTION

The emerging technique of accelerating protons and heavier ions by highly intense laser pulses has attracted considerable interest for its potential to provide compact particle sources [1]. These are especially promising for medical applications where the size and cost of classical accelerators hinder the prevalence of hadrons for cancer therapy. In case of external beam radiation therapy with carbon ions, the energies required for deep-lying tumors are an order of magnitude above the maximum achieved in laser-plasma interactions. Therapeutic applications of laser-driven ion sources are therefore often considered far beyond the current technical possibilities.

The requirement on high ion energies is justified mainly by their range inside the patient. A superficial treatment may well be conducted with low-energy ions with broad energy spread. We propose a new therapeutic modality which combines the versatility of Intra-Operative Radiation Therapy (IORT) with the demonstrated advantages of carbon ions as compared to photon and electron radiation. In order to motivate the new technique we give a brief overview on IORT and current proton and ion therapy in section II. In section III A we review in detail the status of carbon ion acceleration by laser-plasma interactions to investigate the feasibility of medical applications. The novel concept of Intra-Operative Ion Therapy (IOIT) will be presented in section III. The characteristics of carbon ion beams reported in recent experiments are already close to the necessities of the proposed application. We therefore hope to motivate further investigation on this novel concept which may be beneficial for the treatment of a wide range of pathologies.

II. MOTIVATION: RADIATION THERAPY WITH CARBON IONS

A. Intra-Operative Radiation Therapy with Photons

The irradiation of a tumor bed immediately after surgical resection is a widely used therapeutic strategy to eradicate remaining cancerous cells. Several methods exist to apply a well-controlled, elevated radiation dose (typically 10-20 Gy) inside the operation room. Compact, mobile accelerators provide electron beams of several MeV or secondary photons in the 50 keV range. Another popular option is the (temporary) implantation of radioactive sources by automated afterloading devices. The total dose required for IORT is lower than in
External Beam Radiation Therapy (EBRT) because of its direct application to the affected organs. This effect is multiplied by a factor 2-3 increase in biological effectiveness of a large single fraction as compared to conventional fractionation [2]. Nevertheless, effects of late toxicity have been observed as a consequence of the intense radiation boost, especially in IORT with electrons. The intrinsic blood vessels and connective tissue of organs suffer long-term damage, and the irradiation of close-by nerves also increases the risk of late side effects [3]. Therefore an even more localised radiation treatment is desirable, as offered by carbon ions with very limited range. In addition, the increased relative biological effectiveness of these ions allows for achieving similar clinical results with a 3-4 times smaller dose as compared to photons or electrons (see section II.B).

The clinical relevance of IORT has been proven for many different types of cancer, also in direct comparison with standard external beam radiation [3]. It has been studied in depth for breast cancer within the TARGIT-A [4] and ELIOT trials [5], with soft X-rays and electrons, respectively. These revealed similar 5-year survival rates for EBRT and IORT, with lower side effects (e.g., in the skin) for the latter. However, ELIOT claimed an increased risk of local and ipsilateral tumor recurrence (2.5-4.4% for IORT as compared to 0.4% for EBRT), with similar findings in TARGIT-A. For the long-term prospect of the patient the importance of complete resection of cancerous tissues has often been stressed, also in combination with standard IORT. Nevertheless, a more efficient IORT may prove to be especially useful where completely clear margins cannot be achieved, e.g. in the vicinity of critical organs, or even with unresectable, small tumors close to the surface. In these cases carbon ions with very limited range may more effectively destroy all remaining cancer cells without harming other tissues.

B. External Beam Proton and Carbon Ion Therapy

Positively charged ions have been used in EBRT for several decades. As compared to electrons and X-rays they possess several advantageous properties. The most prominent one is the deposition of their bulk energy in the so-called Bragg peak at the end of their trajectory, while the dose in tissues on top of the target volume is minimized. This is expressed by the linear energy transfer (LET) (given in keV/µm) which is highest for low-energy ions. Behind the target no primary ions are present. However, in this region the
dose may be non-vanishing due to projectile fragmentation (in case of $Z > 1$ beams) or the production of other secondary radiation. These effects are important for ion energies of several hundred MeV/$u$ which are necessary to reach penetration depths around 20 cm inside the human body.

Another outstanding feature of positive ions is their capacity to kill malignant cells. For high-LET carbon ions it is about 3-4 times higher than the one of soft X-rays at the same radiation dose while for protons this so-called relative biological effectiveness (RBE) is only increased by 10-15% [6–8]. This implies that the total dose can be reduced by a factor 3-4 to achieve the same cell-killing effect as compared to photon or electron radiation therapy. In a direct comparison the RBE of high-LET carbon ions has been found larger for tumor cells than for skin cells of mice [9]. A further, important advantage resides in the capacity of carbon ions to efficiently destroy hypoxic tumor cells [10, 11] and cancer stem cells [12–14] which show increased resistance to photons, electrons, and protons and are held responsible for local tumor recurrence and the generation of distant metastasis. Further positive effects have been reported such as the suppression of angiogenesis [11]. The overall superior efficiency of carbon ion treatment has been demonstrated for EBRT of several pathologies like adenoid cystic carcinoma, skull base and paracervical spine chordoma, retroperitoneal sarcoma, and non-small cell lung cancer where local control and survival rates are significantly higher than for photon, and even proton, irradiation [15]. Similar conclusions have been reported for various other cancer sites including photon-resistant tumors [16]. These findings underline the necessity to augment the availability of carbon ion therapy and to extend its use beyond deep-lying lesions in order to improve the long-term prospect of cancer therapy.

Existing ion therapy centres are designed to take maximum advantage of the physical peculiarities of these particles. They typically aim at deep-lying, non-resectable tumors for which they are clearly superior to external photon or electron beams. Ion energies are precisely adjusted to reach a given depth. Extended tumors are scanned layerwise with very thin (“pencil”) beams. The direction of the incoming ion beam is varied over time in order to minimize the radiation dose along the entrance path. The technological effort of this kind of treatment is huge. Modern carbon therapy centres, such as the Heidelberg Ion-Beam Therapy Centre (HIT, Germany), are equipped with fully rotating gantries (25 m diameter, 600 metric tons), in addition to the accelerator sections necessary to provide a 400 MeV/$u$, monoenergetic carbon ion beam. Such facilities, with building costs exceeding 100 million
dollars, are affordable only for the most developed countries. At present seven carbon ion therapy centres are operative worldwide, in Japan (at Chiba, Hyogo, Gunma, and Tosu), China (Lanzhou), Italy (Pavia), and Germany (Heidelberg, after a previous pilot project at GSI, Darmstadt) [17]. Approximately 13000 patients have been treated with external carbon ion beams to date.

C. Intra-Operative Ion Therapy: A Novel Concept

Proton and ion acceleration by ultra-intense lasers has been widely discussed as possible means to reduce the size and cost of therapeutic facilities [18]. This emerging technique, detailed in section III A, allows for replacing the large radiofrequency accelerator structures and part of the electromagnetic beam control elements of classical accelerators by much more compact, optical components [19–21]. Despite considerable progress throughout the last decade it has not yet been possible to demonstrate proton or ion acceleration to energies as those applied in EBRT. An intra-operative radiation treatment at ten times lower carbon ion energies which may constitute an opportunity for exploiting the possibilities of laser-ion acceleration on a short time scale. We propose a suitable radiation system as sketched in Figure 1. We will briefly outline its setup and, in the subsequent sections, justify its technical details and study its feasibility.

The general layout is based on typical requirements of IORT. We suppose that an operated tumor bed is accessible from on top of the patient. This is the main direction of the incoming ion beam which is guided by a straight, lean applicator. The device should be capable of irradiating a total area of 30 cm\(^2\) within ten minutes treatment time although the actual size of the lesion may strongly vary with the pathology. The radiation dose applied in IORT usually ranges from 10-20 Gy. With the increased RBE of carbon ions a single boost of approximately 10 Gy throughout a homogeneous dose profile up to 5 mm depth is appropriate.

A fundamental part of the accelerator section is the high-power, Ti:sapphire or Nd:glass laser source (1) with single pulse energy of the order \( W_L = 10 \text{ J} \) and focused intensity \( I_0 = 5 \times 10^{19} \text{ W/cm}^2 \). These orientation values are indicated as shaded areas in Figure 3. Laser pulses (2) are focused (3) on a carbon-rich target (4) within a focal spot of a few micrometers diameter. Carbon ions are released and accelerated in a direction close to the
FIG. 1. General layout of a compact carbon ion irradiation system (components: see text). Inset: Zoom on optical and beam selecting parts.

A copper collimator (6) with 1 msr aperture selects the central part of the beam where ions reach the highest energies. Carbon ions pass a stripper foil (7) of 1 µm thickness to remove remaining electrons and enrich the C⁶⁺ charge state. A pair of dipole magnets (8) with 0.1 Tm field integral is applied to eliminate electrons and to define a minimum accepted energy through a second collimator (9). All these components are housed inside a vacuum system of 10⁻⁵ mbar (10). The accelerated ions pass through a thin kapton window at the end of an applicator section (11). The final beam spot diameter and shape may be adjusted in a third collimator inside the applicator. As typically a relatively large area (of the order of 30 cm²) will be irradiated it is advantageous to use a beam with 10 mm diameter and scan the entire surface. A very narrow pencil beam, which is standard at high-energy facilities, is not required here. Realistically, only this final applicator should be housed inside the operation room. The laser and most of the radiation shielding (12) may be mounted in a separate room with independent cooling system and better accessibility.
for technical maintenance. However, the applicator must provide some flexibility to adjust the beam hit position and angle, an operation which requires reverse interaction on several up-stream components, including the laser target and focusing system and the magnetic momentum selector. A gamma detector (13) based on a high-density, inorganic crystal such as BGO allows for monitoring the applied radiation dose by measuring the activity of isotopes produced by projectile fragmentation and other nuclear reactions inside the patient.

III. FEASIBILITY OF IOIT: MATERIAL AND METHODS

We have addressed several fundamental aspects related to the underlying acceleration technique and the therapeutic characteristics of carbon ions to assess the feasibility and usefulness of our proposed treatment system. The carbon ion energy required for the irradiation of soft tissue up to 5 mm depth is estimated with the common simulation program SRIM [22]. From the calculated ion range in water (Fig. 2) we conclude that a maximum energy of 40 MeV/u (480 MeV) is sufficient for our application. An additional calculation in air shows that carbon ions at these energies may well traverse a few centimetres between the applicator and the patient.

![Carbon ion range in water and air](image)

FIG. 2. Range of carbon ions in water (left) and in air as function of kinetic energy (data from SRIM).

In order to evaluate whether carbon ions of sufficient energy can be provided by state-of-the-art laser-plasma acceleration, and to derive reliable beam parameters like spectral distribution, particle numbers, and angular spread we extensively review the available literature (section III A). The published experimental data allow for estimating the requirements in terms of laser power and preferred target materials as well as a typical ion spectrum from
a single laser shot which is the base for the subsequent studies. We then discuss the beam control elements necessary for the transport of the carbon ions from the laser target to the patient. The outline proposed in section II C requires only few components as compared to EBRT gantries for ion therapy. Its feasibility can be justified by classical arguments (e.g., the bending power of the dipole magnets).

With the aim to demonstrate possible therapeutic applications we have used the GATE V6 code [23] to simulate the dose deposition of carbon ions from a single laser shot with a realistic spectral distribution and angular spread. The depth of the maximum dose is varied by elimination of the low-energy part of the spectra with a suitable collimator. We investigate how a relatively small number of ion bunches with different spectral shape can be superimposed to achieve a uniform dose of 10 Gy over the entire treatment volume. Further, we apply SRIM to calculate the average linear energy transfer (LET) as a function of depth. Since a high LET is necessary to fully exploit the advantageous properties of carbon ions we propose an alternative treatment scheme aiming at constant LET rather than constant total dose. In addition, the GATE simulations give information on nuclear reactions inside the target, especially the production of secondary nuclei. We exploit these data to evaluate the possibility of dose monitoring from PET ($\beta^+$) or single $\gamma$ emitting isotopes.

A. Data for Ion Acceleration by Ultra-intense Laser Pulses

Laser-plasma acceleration of protons and ions requires a high-power (terawatt) laser providing femtosecond pulses which are focused on a suitable target, and detectors for the characterisation of the accelerated particles in terms of energy spectrum, particle numbers, and angular distribution [1]. At focused laser intensities between $10^{18}$ and $10^{21}$ W/cm$^2$ and single pulse energies between 1 mJ and more than 300 J, particles are emitted from a narrow spot around the laser hit position, forming a beam along (or close to) the target normal direction. The ion energies, $E$, are widely spread, and the particle numbers per energy interval can be parametrised by a Boltzmann distribution [24],

$$\frac{\Delta N}{\Delta E} = \frac{N_0}{E} e^{-E/k_BT},$$

up to a sharp cutoff, $E_{\text{max}}$. This maximum energy strongly varies with several experimental parameters like the laser pulse energy and focused intensity (denoted $W_p$ and $I_0$, respec-
tively), the pulse contrast, and the target material and thickness. Only a few percent of the laser pulse energy may be converted into kinetic energy of accelerated ions.

Experimental results on the acceleration of “heavy” \((Z > 1)\) ions currently are much less abundant than those of protons. The reasons for this are threefold: The mass-normalized ion energies (in MeV/u) are lower because the transfer of electrostatic potential into kinetic energy is less efficient for ions with reduced charge-over-mass ratio \((q/m_u = 1/2\) in the best case); the detection and identification of ions, especially at low energies, is more demanding than for protons; and in the presence of protons the acceleration of heavier ions is suppressed. The last point implies the use of high-purity laser targets. Table I provides an overview on experimental data for \(Z > 1\) ions.

An important parameter for possible hadron therapy applications is the number of accelerated ions, especially at the high-energy end of the spectra. Many authors present the number of particles, normalised to ions/(MeV/u)/sr, but collected in a detector with limited aperture, such as a Thomson parabola spectrometer with some nanosteradian acceptance angle positioned along the target normal direction. For a concise extraction of total particle numbers the angular distribution and the useful divergence of the ion beam should be taken into account. To deduce the indicative figures presented in Table I we have assumed a uniform energy distribution up to \(1^\circ\) opening angle (corresponding to \(\sim 1\) msr).

Finally, the population of different charge states of the same isotope is important for possible practical applications. Many authors restrict a detailed presentation of their results to completely ionized states. In Carroll et al. [32] the maximum ion energy is roughly proportional to the charge number when comparing \(C^{1+}, C^{2+}, C^{4+},\) and \(C^{6+}\) ions. Some indications exist that not necessarily all possible charge states are populated and that full ionization of the target material may not always be achieved [29, 30]. These relatively scarce experimental findings require further confirmation.

IV. RESULTS

A. Feasibility of a laser-based carbon ion source

The most critical aspect to assess the feasibility of the radiation device is the reliable acceleration of carbon ions by a highly intense laser source, with sufficiently large ion energy,
TABLE I. Experimental data of laser-accelerated ions with $Z > 1$. Ion numbers are estimations based on published spectra after proper normalisation (see text).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pulse energy $W_L$ [J]</th>
<th>Laser power $P_L$ [TW]</th>
<th>Focused intensity $I_0$ [W/cm$^2$]</th>
<th>Target material species</th>
<th>Ion $E_{\text{max}}$ [MeV/u]</th>
<th>Ion no. at $E_{\text{max}}$ [1/(MeV/u)/msr]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujii [25]</td>
<td>0.088</td>
<td>20</td>
<td>$6.8 \times 10^{18}$ Cu</td>
<td>C</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Kar [26]</td>
<td>200</td>
<td>250</td>
<td>$3 \times 10^{20}$ Cu, Al</td>
<td>C</td>
<td>11</td>
<td>$10^8$</td>
</tr>
<tr>
<td>McKenna [27]</td>
<td>400</td>
<td>1 PW</td>
<td>$2 \times 10^{20}$ Fe</td>
<td>C, Fe</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Willingale [28]</td>
<td>6</td>
<td></td>
<td>$2.5 \times 10^{19}$ Al + polymere</td>
<td>D</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Hegelich [29]</td>
<td>20</td>
<td>30</td>
<td>$1 \times 10^{19}$ Pd+CH$_2$</td>
<td>C</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hegelich [30]</td>
<td>30</td>
<td>100</td>
<td>$5 \times 10^{19}$ Al+C, W+CaF$_2$</td>
<td>C, F</td>
<td>5</td>
<td>$10^6$</td>
</tr>
<tr>
<td>Hegelich [31]</td>
<td>30</td>
<td>100</td>
<td>$5 \times 10^{19}$ metal+CH$_2$/CaF$_2$</td>
<td>C, O, F, Be</td>
<td>5.5</td>
<td>$10^6$</td>
</tr>
<tr>
<td>Carroll [32]</td>
<td></td>
<td></td>
<td>$5.8 \times 10^{20}$ C foil</td>
<td>C</td>
<td>5</td>
<td>$10^8$</td>
</tr>
<tr>
<td>Henig [33]</td>
<td>0.7</td>
<td>30</td>
<td>$5 \times 10^{19}$ DLC</td>
<td>C</td>
<td>6</td>
<td>$10^6$</td>
</tr>
<tr>
<td>Henig [34]</td>
<td>80</td>
<td>100</td>
<td>$7 \times 10^{19}$ DLC</td>
<td>C</td>
<td>15</td>
<td>$10^7$</td>
</tr>
<tr>
<td>Jung [35]</td>
<td>80</td>
<td>1 PW</td>
<td>$5 \times 10^{20}$ diamond</td>
<td>C</td>
<td>54</td>
<td>$10^5$</td>
</tr>
<tr>
<td>Hegelich [36]</td>
<td>90</td>
<td>150</td>
<td>$2 \times 10^{20}$ DLC, CH$_2$</td>
<td>C</td>
<td>44</td>
<td>$10^6$</td>
</tr>
<tr>
<td>Fukuda [37]</td>
<td>0.15</td>
<td>4</td>
<td>$7 \times 10^{17}$ He-CO$_2$ gas</td>
<td>C, O, He</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Willingale [38]</td>
<td>340</td>
<td>1 PW</td>
<td>$5.5 \times 10^{20}$ He gas</td>
<td>He</td>
<td>3</td>
<td>$10^9$</td>
</tr>
<tr>
<td>Fukuda [39]</td>
<td>1</td>
<td>1 PW</td>
<td>$7 \times 10^{18}$ He-CO$_2$ gas</td>
<td>C, O, He</td>
<td>50</td>
<td>$10^4$-$10^5$</td>
</tr>
</tbody>
</table>

particle numbers, and repetition rate. Table-top laser systems with 10 J pulse energy, and 1-10 Hz repetition rate are not current standard, but may be a realistic goal within a few years. To judge whether this is sufficient for our proposed application we consider the experimental review of section III A.

A comparison of data obtained with thin metallic targets [25–27] or metals coated with dielectric materials [28–31] (Figure 3) reveals roughly a $E_{\text{max}} \propto \sqrt{W_L}$ and $E_{\text{max}} \propto \sqrt{I_0}$ scaling of the maximum ion energy per nucleon, similar to what is known from protons in the laser-plasma interaction regime of Target Normal Sheath Acceleration (TNSA) [1].
FIG. 3. Experimental data for maximum ion energies as a function of laser pulse energy and focused intensity. The dotted trend lines correspond to $A \times (W_L/J)^{0.5}$, $A = 0.75 \text{ MeV/u}$ (red) and $A = 4.0 \text{ MeV/u}$ (blue) for (a), and $0.75 \text{ MeV/u} \times (I_0/10^{18} \text{ W/cm}^2)^{0.5}$ (red) and $0.15 \text{ MeV/u} \times (I_0/10^{18} \text{ W/cm}^2)$ (blue) for (b), respectively. The shaded areas indicate a possible range of working parameters for a compact treatment device.

The highest ion energies (44-54 MeV/u) have been achieved with diamond-like carbon targets at petawatt facilities with 80-90 J single pulse energy [35, 36]. Several independent experiments with DLC and dielectric laser targets reveal about 5 times higher ion energies as compared to metal foils (Figure 3). They are attributed to more efficient acceleration mechanisms like Radiation Pressure Acceleration (RPA) and Break-Out Afterburner (BOA) [40] due to lasers with ultra-high intensity and contrast. Although the data are still not too abundant, the general trend indicates indeed a $E_{\text{max}} \propto I_0$ scaling predicted for these regimes.

With gas jet [38] and cluster-gas targets [37, 39] high-energetic ions of different species have been reported, partly at moderate laser pulse power ($\leq 1 \text{ J}$) and focused intensities ($< 10^{18} \text{ W/cm}^2$). It is not clear how the maximum ion energy scales with the laser parameters. Note also that the elemental composition of ions from cluster-gas targets (possibly a mixture of He, C, and O ions) remains unspecified and is not obviously suitable for medical purposes.

We conclude that realistically, 40 MeV/u carbon ions cannot be obtained with much less than 60-80 J single pulse energy, at least with DLC targets. To the contrary, with a gas-cluster target similar maximum energies have been observed with only 1 J per pulse [39], however with much lower particle numbers. Our envisaged working regime (shaded areas in Figure 3) lies between the results obtained with DLC and gas-cluster targets. A good candidate for the acceleration of carbon ions up to 40 MeV/u with 10 J pulses may
therefore be solid, underdense target materials such as carbon foams [41]. However, their suitability requires further experimental confirmation. High purity of the target is critical; protons from hydrogen contaminants hinder the efficient acceleration of carbon ions, and other elemental components (such as oxygen) may be difficult to separate from the particle beam.

The absolute particle numbers around $10^6/(\text{MeV}/u)/\text{msr}$ per shot for energies around 40 MeV/u [36] look rather low. However, as the numbers increase by 1-2 orders of magnitude towards lower energies the total may be 100 times higher, making $10^8$ useful ions over the full spectral range a realistic estimate. The following calculations are based on a generic spectrum following eq. (1), with the energy range and particle numbers similar to the experimental results by Hegelich et al. [36], however with a low-energy cutoff at 100 MeV (8.3 MeV/u) (Figure 4). In section IV A we will show that this spectral distribution allows for a major dose deposition inside the patient. We thus assume an initial beam aperture of 1 msr, defined by the first collimator. Ions at larger angles are absorbed in 5 mm of copper or equivalent materials.

![Generic carbon ion distribution for single laser shot](image)

**FIG. 4.** Generic energy distribution of laser-accelerated carbon ions. The low-energy cutoff (coloured lines) may be adjusted with a collimator located between the dipole magnets.

Further stringent requirements for the laser accelerator are a high repetition rate (around 10 Hz) and a good pulse-to-pulse stability. These presently suffer from severe technical limitations. Terawatt lasers capable of pulse rates $\geq 1$ Hz are still rare. The biggest difficulty resides, however, in the design of a suitable target. For each laser shot a previously unused target area has to be positioned at the focal spot with a 3D precision of a few microns.
Possible technical solutions for some types of materials have been studied [42], but these do not include pure carbon targets. We conclude that both lasers and laser targets require technical optimisation for medical applications, but their development is not complicated by fundamental obstacles.

B. Beam control

The broad energy spectra of the carbon ions and the concurrent acceleration of (hot and cold) electrons behind the laser target necessitate some magnetic beam control elements, albeit much less than in classical accelerators. Their design is challenged by the possible mixture of different charge states. Therefore we suggest to homogenize the ionization spectrum by stripping the remaining electrons off the carbon ions with charge states lower or equal than C\(^{5+}\). This can be achieved with a carbon stripper foil placed directly behind the laser target, similar to injection systems of synchrotrons [43]. Its exact dimensions depend on the composition of the initial beam. Just as a benchmark we have calculated that in a pure carbon foil of one micron thickness, 95% of C\(^{5+}\) ions at 400 MeV (33.3 MeV/\(u\)) are converted into C\(^{6+}\).

The beam is then deflected and redirected inside a pair of dipole magnets with 0.1 Tm field integral each. Note that in a single dipole field (such as a 90° bending magnet which is typical for therapeutic gantries) the spectral components of the beam would be spatially separated. For C\(^{9+}\) ions at 100-480 MeV the deflection angle is between 3.1° and 6.9°. If we suppose a drift length of 200 mm this corresponds to a lateral deflection between 10.8 and 24.2 mm, respectively. A collimator with adjustable slit size behind the first dipole defines the maximum accepted deviation corresponding to the low-energy limit of the ion spectrum. It may be made of 5 mm of copper which is sufficient to absorb ions with energies below the desired minimum. The ion beam is further collimated at the end of the applicator to produce a spot size of 10 mm diameter on the patient. With a total flight path of approximately 3 m from the laser target a major part of the initial beam is lost due to its angular divergence; the corresponding solid angle is only \(9 \times 10^{-3}\) mrad. We therefore propose to install a focusing element behind the second dipole. As was shown by Hofmann et al. [44], a single solenoid (360 mm long, 44 mm inner diameter, maximum field 10 T) can effectively focus laser-accelerated ions, even with a finite momentum distribution. Their
calculations referred to protons at 200 MeV, with a magnetic rigidity of 2.1 Tm, and revealed a 10% transmission efficiency. Low-energy carbon ions (40 MeV/u) possess a similar rigidity (1.8 Tm) and therefore may be focussed in a solenoid of this size and field strength. For the scope of the present proof-of-principle study we thus assume that 10% of the ions initially emitted in 1 mrad will be useful for irradiation of the patient.

A major concern for radiation treatment is the safety of the patient and the operating staff. In the laser-plasma interaction not only carbon ions are released, but also electrons and X-rays. With the laser section housed in a separate room effective shielding can be provided for all kinds of secondary radiation. Direct X-rays from the laser target are absorbed behind the first chicane magnet. In the same dipole, electrons are deflected opposite to the carbon ions and eliminated by absorbers. Thus, a pure carbon beam is provided in the applicator section. The unwanted part of these ions (at large angles) is completely absorbed in a few mm of medium-dense materials such as copper. In total, the use of low-energy carbon ions can be considered a safe technique which may be applied in the presence of the operating personnel.

C. Treatment application

With the aim to demonstrate possible therapeutic applications we have used the GATE V6 code [23] to simulate the dose deposition in water of $10^7$ carbon ions from a single laser shot, with a spectral distribution between 100 and 480 MeV (8.3-40 MeV/u) as shown in Figure 4 and concentrated in a uniform beam with 10 mm diameter (Figure 5(a)). The maximum radiation dose at a depth of 0.4 mm is approximately 6.5 Gy, decreasing rapidly for deeper-lying tissue, dropping to 0.6 Gy at 2 mm depth. At more than 5 mm inside the patient, the single-shot dose due to fragmentation of the carbon ions or other, secondary radiation is below 0.025 Gy. Note that in photon or electron IORT a major part of the total dose is deposited behind the target volume, limiting the applicability of the technique in the vicinity of critical organs. To illustrate the very distinct properties of carbon, electron, and photon beams we have also calculated dose-depth profiles of monoenergetic, 3 MeV electrons and 50 keV photons as typically used in IORT (Figure 5(a)).

The strongly peaked dose deposition of the full spectral range, with its maximum very close to the surface, may not straightforwardly correspond to the necessities of the treatment
FIG. 5. (a) Dose profile as function of depth in water for $10^7$ carbon ions with spectral distribution following Figure 4, compared to monoenergetic electrons and photons. (b) Dose profiles of carbon ion spectra with different minimum energies, weighted with individual numbers of shots. Colours correspond to the low-energy limits of Figure 4. The thick line refers to the weighted sum.

A more uniform profile can be obtained by subsequent irradiation with multiple laser shots of different minimum energies. As illustrated in Figure 5(b), the peak of the dose profile moves to larger depths as the low-energy cutoff increases. In the high-energy regime increasing numbers of pulses are required. Note that ion intensities corresponding to fractional numbers of shots (in our example for the full, 100-480 MeV interval) can be realised by manipulation of the first collimator. The sum of all laser shots (thick black line) at a level of 10 Gy is constant within 10% up to 4.4 mm depth. An even more uniform profile can be achieved by a larger number of intervals. Note that in photon and electron IORT typically 10-20 Gy are applied in a single irradiation. For carbon ions the same biological effect can be obtained at lower dose due to the increased RBE value.

These GATE simulations demonstrate that laser-ion spectra of finite width can be superposed to obtain a uniform dose deposition inside a given target volume. Note that this treatment scheme is very different from the layerwise scanning with mono-energetic pencil beams which is the standard technique at external beam facilities. Similar results have very recently been obtained for laser-accelerated protons at EBRT energies [21]. In our example a total of approximately 180 shots is required to irradiate a circular area of 10 mm diameter. This implies that a pulse rate of 10 Hz is necessary to accomplish the stepwise irradiation of a 30 cm² wide operated bed within ten minutes.
D. Control of applied dose

The superficial radiation dose, applied by a single shot of carbon ions as described above, approaches locally more than 5 Gy for $10^7$ particles, albeit confined to a very small volume. The overall number of pulses required to irradiate a given area is quite limited. This implies that, for dose control purposes, the shot-to-shot stability of ion energies and intensities must be guaranteed up to a few percent. Apart from separate control measurements (performed before an intervention) the radiation can be monitored directly. Since the accelerated beam has a relatively large aperture part of the off-axis (halo) ions can be detected and characterised, e.g. directly in front of the last collimator.

Some of the incident carbon ions undergo nuclear reactions and produce $\beta^+$ isotopes which 511 keV annihilation photons can be detected with Positron Emission Tomography (PET) systems for a spatial reconstruction of the dose deep inside the patient. This technique is well known in External Beam Radiation Therapy [45]. In order to verify its feasibility at much lower ion energies we have estimated the yield of $\beta^+$ nuclei as follows. The cross section of the $^{12}\text{C}(p,np)^{11}\text{C}$ reaction is approximately 80 mbarn for a proton beam with $E_p = 25-40$ MeV hitting a carbon target [46]. In inverse kinematics this corresponds to 25-40 MeV/u carbon ions incident on protons. Taking into account the range and energy loss of the ions in water, a spectral distribution like the one of Figure 4(a) (with 200 MeV minimum energy) translates into approximately 3000 $^{11}\text{C}$ nuclei produced from $10^7$ incident $^{12}\text{C}$ ions. Their $\beta^+$ activity is only 1.7 Bq which is insufficient for a reliable monitoring.

Further information on the production of $\beta^+$ isotopes can be obtained from the GATE simulations mentioned in the previous section which provide a list of all nuclear fragments. For the simulated absorption of carbon ions in water these include the $^{12}\text{C}(p,X)$ and $^{12}\text{C}(^{16}\text{O},X)$ reaction channels. Again, for a single shot of $10^7$ carbon ions with 200 MeV minimum energy we find between 400 and 4000 atoms of different PET isotopes with a $\beta^+$ activity of 12 Bq, the most important contribution coming from $^{15}\text{O}$. Even if more activity is accumulated with each pulse a precise dose control by this method is quite demanding. However, for a superficial therapy the 3D reconstruction is not required and thus it may be more efficient to detect only single, 511 keV annihilation photons inside a predefined energy interval instead of requiring a pair coincidence. However, taking into account the finite (small) aperture of a gamma detector the count rate will still be too low for a precise
Nevertheless, an alternative way of monitoring looks feasible, based on direct gamma decays of $^{12}$C reaction products. The GATE simulations indicate, for example, the production of two excited states of $^{24}$Mg, with about 570 atoms each, which immediately decay to the ground state by emission of 1.37 MeV and 2.76 MeV photons. The appearance of this isotope is plausible from the $^{12}$C + $^{16}$O → $^{24}$Mg + α fusion channel. These energetic photons may efficiently be identified with an inorganic crystal (say, 60 mm of BGO) close to the irradiated area. We therefore propose to include such a detector in the layout of the treatment system.

V. CONCLUSIONS

Ion acceleration by high-intensity laser pulses may provide carbon ion beams of sufficient energy and particle numbers for superficial radiation treatment in the near future. Several key aspects of this underlying technique have been demonstrated at various high-power laser facilities worldwide. While the maximum carbon ion energies are an order of magnitude below the necessities of EBRT facilities for the irradiation of deep-lying lesions the characteristics of laser-accelerated carbon ions may be exploited in a completely new treatment modality, Intra-Operative Ion Therapy. We sketch the basic outline of a proposed therapy device which is sufficiently small for installation in a hospital and address several key aspects of its successful operation. It consists of two major sections, an applicator inside the operating room and the laser-ion accelerator housed in an adjacent room for better accessibility and shielding of secondary radiation.

A review of published data on laser-accelerated carbon ions reveals that maximum carbon ion energies around 40 MeV/u, as required for superficial irradiation up to 5 mm depth, have already been achieved, however at large-scale laser facilities. Typical ion spectra are broad with exponentially dropping particle numbers towards higher energies. A total of $10^8$ carbon ions have been reported within 1 msr solid angle towards the target normal direction. Similar results may be feasible with laser pulse energies in the 10 J range by use of low-density target materials of high purity such as carbon foams. Further basic research is required to confirm this conclusion. For homogenization of ion charge states we propose the implementation of a thin stripper foil.
We derive several technical necessities related to ion beam transport in the proposed therapy device. These are by far less stringent than those of EBRT facilities for irradiation of deep-lying tumors. For superficial lesions like recently resected tumor beds a fully rotating gantry is not required. The carbon ions are administered through a straight applicator on top of the patient, albeit with some angular flexibility. Thereby we take advantage of the initial momentum direction and spare large bending magnets. The only indispensable beam-optical elements are a pair of dipole magnets, with 0.1 Tm integrated field strength each, for the selection of finite momentum intervals in conjunction with adjustable collimators. These also guarantee the elimination of electrons from the laser-plasma interaction. In addition, focusing in a single solenoid may be advantageous to reduce the loss of carbon ions due to angular spread.

In GATE simulations we have shown the dose deposition of carbon ions from a single laser shot to be limited to a maximum depth of 5 mm, contrary to photon and electron radiation in current IORT. Despite the broad initial energy spread a uniform dose profile may be obtained by superposition of several pulses with distinct minimum energies. We deduce that 10 Hz repetition rate is required for the complete irradiation of a 30 cm$^2$ wide area within ten minutes. This is feasible for present-day high-power lasers, but still a challenge for the construction of suitable laser targets. In addition, we have critically evaluated the possibilities of monitoring the applied dose and concluded that the detection of prompt $\gamma$ rays is the most promising alternative whereas the production of $\beta^+$ (PET) isotopes, preferred in current carbon EBRT, is insufficient due to reduced ion energies.

With the proposed, intra-operative treatment scheme it will be possible to exploit the elevated biological effectiveness of carbon ions for a large number of cancer patients. The aim is to provide a sufficiently compact device to be used at local hospitals, contrary to the huge therapy centers of today. The medical benefits will require numerous studies. Conceptually, IOIT does not intend to fully replace photon and electron IORT; many aspects, including practicability, cost effectiveness, treatment efficiency, and side effects, will have to be assessed for many pathologies on a long-term scale. IOIT does not even compete with external-beam carbon ion therapy at high energies because the treated tumor sites (superficial vs. deep-lying) are completely distinct. IOIT may thus be established as an independent treatment modality and, at the same time, promote research on laser-ion acceleration for medical purposes.
ACKNOWLEDGMENTS

This work has partially been funded by the Centre for Industrial Technological Development (CDTI), ref. IPT-20111027, through the Science Industry Subprogramme.

Conflicts of interest: All authors declare that they have no conflicts of interest.


