What will it take for laser driven proton accelerators to be applied to tumor therapy?

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After many years on the periphery of cancer therapy, the successes of proton and ion beams in tumor therapy are gradually receiving a higher degree of recognition. The considerable construction and acquisition costs are usually invoked to explain the slow market penetration of this favorable treatment modality. Recently, high-intensity lasers have been suggested as a potential, cost-saving alternative to cyclotrons or synchrotrons for oncology. This article will detail the technical requirements necessary for successful implementation of ion beam therapy (IBT)—the general term for proton and heavier-ion therapy. It will summarize the current state of laser acceleration of protons and will outline the very substantial developments still necessary for this technology to be successfully applied to IBT.

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I. INTRODUCTION

Sixty years after Robert Wilson's initial proposal to use fast protons for radiotherapy [1], the physical advantage of the Bragg peak inherent in slowing protons and ions is undisputed. However, despite encouraging results and about 50 000 patients treated, IBT still leads a niche subsistence in cancer therapy (for reviews, see [2–4]). High capital costs of proton-therapy installations—and even higher costs for carbon-ion facilities—are most often cited as the primary hurdles to more widespread application.

Recently, IBT has been receiving unexpected promotion from researchers of the high-power laser community [5–12]. These authors typically state that the use of ultraintense lasers rather than conventional particle accelerators could provide ''compact, flexible and cost-effective'' therapy facilities, fostering the propagation of IBT. Several authors imply that the technology is quite close to being ready for direct application in the field [9].

Lest untimely promises be made and the medical community prematurely rush to this new and exciting technology, we wish to point out some very substantial hurdles still facing laser accelerators before this technology can be successfully applied to generating ion beams adequate for radiotherapy in human patients. To do this, we will discuss in depth the very exacting beam requirements to ensure optimal deposition of the prescribed dose, allow accurate dosimetry and verification of dose delivery, minimize the dose to areas outside the desired treatment volume, and assure patient safety from accidental overdoses.

It should first be stated quite categorically that it has taken years and decades for conventional accelerators to achieve the above beam qualities that ensure the present success of IBT. As will be pointed out, the task of lasers to match the capabilities of conventional accelerators in this field is a truly huge one, and practitioners in the field must not be tempted to lose sight of the tremendous task at hand before making misleading claims that can raise expectations within the medical community.

II. BACKGROUND: DEVELOPMENT AND CURRENT STATE OF IBT

The search for higher precision and greater antitumor effectiveness has been the driving force in the history of radiotherapy. After the discovery of the favorable depth-dose profile of protons and other ions by Robert Wilson at what later became the Lawrence Berkeley Laboratory (LBL) in Berkeley, USA [1], it only took a few years until the first clinical application. It was John Lawrence who used protons from the LBL cyclotron for pituitary hormone suppression in patients with metastatic breast carcinoma [13]. Functional stereotactic radiosurgery in the brain and fractionated proton therapy of large tumors were soon to follow in Uppsala, Sweden, and at the Harvard Cyclotron Laboratory in conjunction with the Massachusetts General Hospital in the USA. Until 1990, when the first hospital-based proton therapy center opened its doors in Loma Linda, California, IBT was only offered in 10 physics laboratories around the world (for a review on the early history on IBT cf. [14]). Today, the number is up to 27, with 11 facilities being hospital based. Three more clinical IBT centers will become operative within the next 12 months and at least six more have been commissioned.

Approximately 50 000 patients have been treated with ion beams, the vast majority ($>90\%$) with protons. During the first decades relatively rare diseases were treated for which there were no real alternatives (e.g., arteriovenous malformations, uveal melanomas, chordomas, chondrosarcomas). At present IBT is used to treat tumors in nearly all parts of the human body (for recent reviews, see [3,4,15]).

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Although IBT has been available for more than 50 years, it is still a relatively uncommon treatment modality. Many technological advances of the past 30 years were necessary to make full use of the favorable physical characteristics of ion beams. Prior to the advent of computer tomography, e.g., tumor imaging and localization did not permit resolution in the millimeter range. As a consequence, dose volumes had to be kept much larger than medically necessary and technically feasible by IBT. Therefore, the superior dose distribution of ions could not be fully exploited at that time. Magnetic resonance imaging, new developments in beam delivery, and computing have all helped to make better use of the physical properties of ions.

The fact that IBT was initiated in physics laboratories is probably another reason for its slow spread. Beam time for medical applications was limited in these laboratories and often had to be shared with the nuclear physics programs. As the institutions were lacking the most basic clinical environment, the patients had to be able to tolerate the treatment sessions without too much assistance and clinical support. This made patient recruitment difficult and restricted the treatable diseases to indications for which there were no real alternatives.

Gradually, it became recognized that IBT yields results which can compete with the most advanced x-ray techniques, even though the treatment conditions in most centers are still suboptimal (e.g. fixed beam direction, mechanical beam spreading). Advances such as beam scanning, respiration gating, intensity modulation, etc., make ion beams even more attractive for therapy, enabling full exploitation of the physical advantages and reduction in the irradiated volume to only what is clinically necessary. Industry, which ignored the field for many years, seems to recognize IBT as well as an upcoming market. There are now several companies which offer turnkey IBT units (IBA, Siemens, Varian/Accel, Hitachi, Mitsubishi, and Optivus).

III. BEAM REQUIREMENTS FOR IBT

Producing beams of high-energy particles is accomplished by many types of accelerators, including now high-power lasers. However, a raw beam is a powerful and highly dangerous tool; it must be carefully shaped and controlled before it can be safely and effectively used for radiation therapy (RT). In addition to the control of transverse dose distribution (lateral field shaping) required for x-ray RT, IBT has—because of the Bragg peak—the need to accurately control the stopping point of the beam. This added dimension contributes to the complexity of IBT.

In the following we will outline the specific characteristics of ion beams necessary to produce well-defined and effective radiation fields. We will describe a specific requirement, how this is met with current-technology accelerators, and the present state of laser-driven accelerators in this area.

IV. BEAM ENERGY

The 25 to 30 cm range in tissue is viewed as the most basic requirement for an ion beam. This translates to 200 to 225 MeV protons, and 400 to 430 MeV/amu carbon ions. This energy must be available at the surface of the patient, so if beam spreading or shaping techniques are employed that require passing the beam through material, the primary energy from the accelerator must be increased further to compensate for energy lost in these devices.

A. Status: Conventional accelerators

Compact normal-conducting proton cyclotrons of 235 MeV are approximately 4 meters in diameter, superconducting cyclotrons can be somewhat smaller.

Proton synchrotrons of 250 MeV are larger, approximately 10 meters in diameter, but are much less massive and overall are more efficient in beam utilization. All of these accelerator types are now commercially available as ''turnkey'' clinical facilities from major manufacturers, with beam-delivery systems and fully-tested control systems. They have been thoroughly reviewed and approved by national health-management organizations [16]. Carbon-ion beams of the required energy are best produced with synchrotrons; the higher energy and rigidity of these beams require considerably larger rings, typically 20–25 meters in diameter. Three such facilities dedicated to IBT are operating today. Several more are being built and will be operational in coming years [17].

B. Status: Laser accelerators

The highest published energy obtained for protons is 58 MeV, with a very large high-power, high-energy laser system at the Lawrence Livermore National Laboratory [18]. The smaller lasers being highlighted as the precursors of the technology path proposed for medical applications have not produced protons higher than about 10 MeV.

The excitement in the field has come from the advances allowing production of extremely short pulses, condensing the energy from modest lasers into extremely high instantaneous power. Thus, instead of kilojoule lasers with picosecond pulses (such as used for the above-cited 58 MeV experiment), lasers with a few joules can produce, by use of pulse-compression ''chirping'' techniques, femtosecond pulses in the 10–100 terawatt range. There is a clearly defined correlation between the instantaneous power in the laser-pulse striking a solid target and the energy of protons accelerated from the back side of this target. Modeling studies and scaling extrapolations indicate that an increase of laser energy by about a factor of 10, with the same or slightly improved pulse-compression techniques, could produce protons of 200 or more MeV [10]. It is assumed that developments in the next few years should yield commercially available lasers of the required energy. However, the major step remains to verify the scaling

laws over such a large extrapolation. The physical systems are highly complex with instabilities and uncertainties. It is by no means certain that placing the higher-power pulse on the target will lead to the desired energy of protons at the required flux.

V. ENERGY VARIABILITY AND MONOCHROMATICITY

The basic $1/E$ dependence of the energy loss curve of an ion beam implies that producing the desired dose at every depth of the treatment field requires extremely precise control over the energy of the beam, and of the flux at each energy level. Treatment planning will ultimately deconvolve a dose in each voxel of the treatment volume to a flux at each lateral $\{x, y\}$ coordinate, and an energy spectrum to yield the correct dose as a function of depth $\{z\}$. This implies control of the energy distribution of pulses at each $\{x, y\}$ coordinate to within a few percent. Range straggling and multiple scattering limit the accuracy of dose deposition, but appropriate treatment planning can take these into account and still obtain dose distributions within a few percent and dose falloffs of a few millimeters.

A. Status: Conventional accelerators

Energy spread of a beam emerging from the above-mentioned accelerators will be of the order of 0.1% $\Delta E/E$. This is a regular property of accelerators of this type. Any higher energy spread would cause too much beam loss inside the accelerator, and almost no beam would reach the final extraction energy. This very narrow energy spread also provides for efficient beam transport from the accelerator through the highly complex gantry transport system, which allows the beam to enter the patient from almost any angle. The high precision of the beam energy warrants that the final width of the Bragg peak is not impaired beyond the contribution of range straggling [19,20].

Energy variability is slightly more complicated. With a synchrotron, it is possible to flattop the magnetic field at the desired energy and extract the pulse at this energy, so each cycle of the synchrotron can produce a beam of protons or ions of a different energy, over the full prescribed range for the treatment. Pulses of the desired energies are superimposed to produce the required depth-dose profile in a tightly controlled fashion.

Obtaining the necessary depth-dose profile with a cyclotron beam is more complex since the beam emerges always with the same energy from the accelerator. To produce lower-energy beams, the protons are passed through an energy-degrader system consisting of a variable-thickness foil, and a magnetic spectrometer and collimation system. Though substantial angular spread is introduced due to scattering in the foil, the collimators select the beam emittance necessary to be transmitted to the patient. Sufficient intensity reserve is available in the cyclotron to compensate the beam loss and to ensure a satisfactory dose rate at the patient. The result of this process is the same very tightly controlled dose-energy profile of the beam delivered to the patient.

Early accelerator systems that lacked the sophisticated energy-variability techniques now available were still able to achieve relatively good depth-dose distributions using monochromatic beams and wedge or ridge filters as part of the final beam-delivery system [20]. Though still employed in many IBT installations, this technique does not give the best dose distributions IBT is capable of. As scanning systems come into wider use, these devices are being phased out.

B. Status: Laser accelerators

Unfortunately, the proton pulses from a laser target are far from monochromatic. Usual energy spread is 100%, with only a small fraction of the total flux at the highest energy [9]. Progress is being made to improve this, with shaped targets to maximize the proton flux in a narrower forward cone [6,7]. A small dot of PMMA (polymethyl methacrylate) or other proton-rich material on the back side of the target, lining up precisely with the laser-pulse center, can substantially increase the localization of emitted protons to a well-defined area, where the electron-blowoff field is at its highest uniformity. Best results to date have yielded an energy spread of about 25% FWHM, but still with considerable low-energy tails, and relatively low proton flux [6].

As indicated above, accuracy in dose-delivery relies on excellent control over the full range of energies required for the treatment, and of the flux at each energy. Controlling the maximum energy of protons from a laser-pulse will require careful control over the power and stability of the laser system, to a degree which appears not to be within current operational experience [8,10]. Shot-to-shot tunability, reproducibility, and predictability must be improved to a level of a few percent! If, in addition, micron accuracy is required for the positioning of microdots in a target to line up precisely with the center of the laser pulse, at a high repetition rate, the problems become more difficult to solve.

One method for ensuring safe, reliable operation of such a system would be to place the laser accelerator at the same location of the present cyclotron or synchrotron, to use the very restrictive beam transport system to allow only the particles of the right characteristics to be transported to the treatment room. However, this would completely defeat the basic premise of compactness of the new technology, and would almost surely not be capable of adequate dose rates. Designing energy-selection spectrometers suitable for use with laser systems is proposed by several authors [21,22], however, the large divergence of the beams and high rigidity makes such spectrometers extremely difficult to design properly, as well as quite large; interfacing these

with a patient delivery system would create a device not unlike the size of the present-day gantries.

If one looks at the energy spectrum of an actual beam used in therapy, the so-called ''spread-out Bragg peak'' (SOBP), it does indeed have a very large energy spread. One might argue that this is not so unlike the energy spread from a laser-accelerator pulse. Indeed, if the maximum energy of the protons were reproducibly and reliably controllable, and if the pulse-to-pulse energy spectrum were controllable and reproducible to within a few percent, it would probably be possible to design a mechanical filter, akin to those used in the early days of IBT, to adjust the spectrum from this pulse to the desired spectrum for a given SOBP. These stability and controllability requirements are very likely difficult challenges for the laser accelerator, and as indicated above would only produce a technology that is a generation behind the scanning technique.

VI. BEAM INTENSITY

Treatment times must be kept to a maximum of a few minutes. Immobilization issues, patient comfort, but also ''customary practice'' with current RT technologies indicate that longer treatment times would render new technologies unattractive and uncompetitive. A treatment of an average volume of approximately 1 liter to a dose of 2 Gy in 1–3 minutes requires of the order of 10^{12} protons, translating to about 10^{10} protons per second as the required flux at the treatment site.

A. Status: Conventional accelerators

10^{10} protons per second corresponds to about 2 nanoamperes of continuous beam. Normal cyclotrons can produce beams of many microamperes, specialized ones even in the milliampere range. The required fluxes are, therefore, easily obtainable. They are also adequate to be detected by normal beam-diagnostic instrumentation, so control and feedback of the accelerator parameters are easily achieved.

Synchrotrons can easily capture and accelerate 10^{10} protons in an acceleration cycle, and with a cycle rate of about 0.5–0.3 Hz can match quite closely the requirements for IBT. Well-designed and tuned synchrotrons in this energy range can accelerate and extract 10–100 times this amount of beam. Pulse-to-pulse energy variability and beam-current control enable excellent contouring of the energy and dose profile to the required delivery prescription.

B. Status: Laser accelerators

Published data on total proton flux from a single pulse are from around 10^9 protons for a broad spectrum [10] to 10^8 protons from a shaped target with a peak energy well below 10 MeV [6]. Achieving the required flux of 10^{10} protons per second will require a repetition rate of at least 10 Hz. The current generation of lasers is in principle capable of this, but most of the literature describes experiments at very low repetition rates. The next generation of lasers, predicted to produce protons of the required energy, is also advertised to be able to operate at 10 Hz. It is essential that these new laser systems at least match the protons-per-pulse performance of today's systems.

It should be remembered that the 10^{10}-protons/s specification is at the site of the patient, not at the exit of the accelerator. In the case of conventional accelerators and modern scanning systems, almost 100% of the beam, once energy selected and formed, can be transported and used in the treatment field. It is not clear what the efficiency of proton utilization with laser accelerators can be to ensure conformation to a prescribed treatment dose distribution. The implication of this is that the required flux from the laser systems should be substantially higher than 10^{10} protons/ sec .

Finally, operating a laser accelerator at 10 Hz will require very sophisticated target-handling and reaction-chamber engineering, to ensure clearing of debris from previous shots, and enabling the micron precision in target positioning for shaped targets that will probably be necessary [22,23].

VII. LATERAL FIELD DEFINITION

The greatest advantage of IBT is the ability to conform the radiation field to very precisely defined contours of a prescribed treatment volume. For truly parallel beams, lateral dose falloff at the edge of the field is dominated by multiple scattering in the patient. A well-designed IBT delivery system will not contribute to this dose falloff beyond what is physically possible. Lateral dose 90%-to-10% falloff—or ''penumbra''—of about 1 cm at depth for protons, and a few mm for carbon ions yields treatment plans that are superior in sparing of tissue outside the prescribed volume to the most sophisticated photon techniques [2,24].

A. Status: IBT systems based on conventional accelerators

Spreading the beam extracted from the accelerator by passive scattering systems is simple and effective for producing flat fields. But such systems increase the emittance of the beam substantially, which leads to loss of precision in lateral falloff by as much as a factor of 2 over the physical limits.

The state of the art for IBT now employs magnetic deflection of the pristine beams via a spot- or raster-scanning system. The amount of matter the particles pass through on their way to the patient is kept to an absolute minimum. This maintains the excellent emittance of the beam from the accelerator, yielding the lowest-possible lateral penumbrae.

B. Status: Laser accelerators

Protons from a laser accelerator all emerge from a spot size about 1 μm in diameter, at a typical divergence of approximately half a radian or 23°. Because of the extremely small spot size, the transverse emittance, $\{\Delta x \times \Delta\Theta\}$, is substantially smaller than the beam from a conventional medical accelerator.

Such a beam could in theory be converted into a good-quality pencil beam by a suitable beam transport system. However, the transport system that will take a beam with such a wide opening angle will be quite large and cumbersome. In addition, most such systems are magnetic, and so very sensitive to the energy of the particles, and the extremely high-energy spread of the raw beam from the laser target would render the design of such a transport system nearly impossible.

The longitudinal emittance of the laser-produced beams is also phenomenally low, because of the small product of the energy spread and the time width of the beam. As the laser pulse is measured in tens of femtoseconds, even with a 100% energy spread of a 10 MeV beam the longitudinal emittance will be substantially smaller than that from a conventional accelerator. In principle, by use of a ''buncher'' (a special-purpose radiofrequency accelerating cavity), the narrow time width can be traded into reduced energy spread. In simple terms, particles emerging from the source at a higher energy reach the buncher placed a distance away (typically a few meters) earlier than the lower-energy ones, so if the accelerating gradient in the buncher changes appropriately with time the high-energy ones will be slowed while the slower ones are speeded up. The practical problem is that bunchers work very well when the energy spread is a small fraction of the total; in the case of the high-energy spread of the ion beam from a laser, the size and length of the buncher would match a full conventional accelerator.

The bottom line is that, though the emittances of particle bunches produced by laser acceleration are very favorable, the hardware necessary to match these beams to a therapy scanning system is unwieldy, expensive, and impractical.

But, does one need all these actions on the beam from the laser accelerator to be able to use it for IBT? We have indicated above that the number of protons in a given element of the treatment volume, both stopping and traversing, must be tightly controlled. It is difficult to see how the energy spectrum, and the lateral distribution of the plume from a laser target, can be made to correspond to the prescription for each of the thousands of volume elements (voxels) in the treatment volume without a very significant amount of control and modification.

VIII. DOSE CONFORMATION

The most desirable characteristic of a radiation therapy modality is to be able to deliver radiation as close as possible to the ideal envisioned by the radiation oncologist. This usually means placing the optimal therapeutic dose into the diseased area, and avoiding as much as possible any irradiation of other areas of the body. One of the biggest advantages of IBT is its potential to accomplish this in a fashion superior to the most advanced photon therapy techniques. The word ''potential'' is important here because the key to achieving this goal lies in how the particle beams are actually delivered to the patient. A highly flexible source of particles, in which intensity, spot size, position, and energy (depth) is finely controlled, offers by far the greatest chance to meet this ideal.

Considering the rapid advances made with photon delivery such as intensity modulated radiation therapy, the true advantages of IBT can only be realized with the most sophisticated delivery systems offering maximum flexibility. Any source of protons that does not offer the same flexibility to develop an optimized plan making full use of the advantages of particles, will not be competitive with conventional photon therapy.

A. Status: IBT with conventional accelerators

Cyclotrons (with external energy-selection systems), and synchrotrons are capable of changing the energy of the beam within seconds. The first scanning systems using these conventional accelerator sources are already in routine use. Commercial vendors are on the verge of marketing fully integrated scanning systems. It is, therefore, fair to say that conventional technologies are close to providing the flexibility in beam parameters to ensure optimal delivery of charged particles [25,26].

B. Status: Laser accelerators

As described above, the energy spread and beam characteristics expected for a laser-generated beam of protons is quite far from the ideal monochromatic pencil beam. To make use of the compactness of the laser systems, the proton-producing target should be relatively close to the treatment area and complex, heavy spectrometers should not be used. Thus properly shaping and controlling the laser plume before it reaches the patient will be difficult. It is our view that with such a beam there is little hope that an attractive treatment plan can be generated.

IX. DOSE ACCURACY AND DOSIMETRY TECHNIQUES

Once a plan is made, it is important that the actual delivery be carried out in a safe, accurate manner. Specifically, the dose delivered to each voxel of the treatment volume should match the prescription to within an error of at most $\pm 5\%$. This is easily achieved by RT technologies in use today with both photons and particles.

To achieve this, one must have a very high degree of control over the accelerator and transport parameters, have explicit trust in the reliability, accuracy, and reproducibility

of these parameters, and, in addition, have reliable, accurate dose-monitoring systems capable of verifying the delivered dose and to quickly terminate a treatment when anything unusual is encountered.

A. Status: IBT with conventional accelerators

In cyclotrons the beam emerges continuously and can be controlled to an extremely precise degree. Synchrotrons provide a ''slow spill,'' enabling a duty cycle of 25% to 50% and a relatively uniform beam during the extraction time.

Accurate dosimetry is usually provided with ionization chambers, whose response is linear as long as the instantaneous dose rate is not so high as to cause gas recombination. The continuous ion flux offers a safety factor. Should an abnormality occur, the fast response time of the ion chambers allows beam interruption to occur before an unacceptably high dose has been delivered erroneously. This is true even for the worst case of a pencil-beam scanning system where beam is being concentrated in a single voxel at the time the interruption is initiated.

B. Status: Laser accelerators

For an accelerator system which delivers beam in short pulses, dosimetry values, including possible error conditions, are recorded only after all the particles of a pulse have entered the patient. The only condition in which this type of operation will have an adequate degree of safety is when the dose delivered in a single pulse is less than a few percent of the total dose for the area treated. If one considers a 10 Hz system, and a treatment time of 100 seconds, there will only be 1000 pulses for a full treatment. If treatment delivery is such that the whole field is irradiated with each pulse, then an error with a single pulse will have little consequence. However, the most optimized treatment delivery techniques rely on sweeping small-dimension beams, so that at any given instant only a small fraction of the treatment volume is being irradiated [25,27]. Under these conditions, a single pulse is important.

For instance, let us assume a treatment volume of 1 liter divided into 1000 voxels of 1 cc. The delivery system would have to provide the entire dose to a voxel in a single pulse! In order to guarantee that a voxel is not overdosed or underdosed, the flux in each beam pulse must be controlled to the level of 5%. Considering the 50% reproducibility quoted in the current laser-accelerator literature [6], achieving this accuracy will be an ambitious task.

X. ISOCENTRIC DELIVERY

The vast majority of patients are treated in a supine position. Not only does this provide maximum comfort for the patients, improving immobilization, but it also coincides with the position in which diagnostic scans are taken. As precise knowledge of coordinates of organs, target volumes, and other body structures is critical in developing accurate treatment plans, it is imperative to treat the patient in the same position in which the diagnostic scans are taken.

For greatest flexibility, optimal beam delivery is achieved when the therapy beam can be aimed at the supine patient from any angle in a vertical plane, while freedom to rotate the patient about the vertical axis allows not only full access to normal entry angles, but also oblique ports, often invoked to avoid critical structures.

A. Status: IBT with conventional accelerators

Vendors of hospital-based proton-therapy systems now offer gantry and patient-positioner systems that provide flexibility of entry angles. The systems are large, heavy, and expensive [28]. The situation is extreme for carbon ions. For example, the isocentric gantry developed for the Heidelberg facility weighs about 600 tons, has a diameter of approximately 15 meters, and is 25 meters long [29]. In addition, large expanses of concrete shielding are required, as the gantry is located inside the vault of the treatment room. It has been recognized that new designs are necessary to reduce size and cost of this component of the beam-delivery system [30].

B. Status: Laser accelerators

The possibility of bringing laser beams into the treatment room and to redirect them with mirrors to a target that can be rotated around a patient is truly attractive [9,11,22]. The key to successful application will be how close the target can be placed to the patient, or how much room will be needed for beam-forming and dosimetry systems to ensure reliable, accurate, and effective treatments. The worst possible scenario would be that beam-control hardware for energy selection, focusing, and steering require the proton source be far away, and the net size of this hardware would not be that different from today's conventional gantries. At the present time, it is difficult to imagine that this would not be the case.

XI. RADIATION PROTECTION, ENVIRONMENTAL CONSIDERATIONS

Though the patient is receiving a significant radiation dose, it is important to restrict this dose to the treatment volume. Control of extraneous radiation sources is very important.

A. Status: IBT with conventional accelerators

Beam transmission in the gantry transport system is carefully monitored to minimize beam loss. Collimation is provided to prevent scattered beam from reaching areas of the patient outside the intended treatment zone. Beam loss in these collimators and other areas will lead to neutron production, to which the patient is exposed.

Calculation and measurements indicate that dose from these sources is an extremely small fraction of the treatment dose [31].

B. Status: Laser accelerators

More than 40% of the laser energy is converted to relativistic electrons, causing hard-x-ray bremsstrahlung and neutrons [18,32]. In fact, neutron production is so high that ultraintense lasers have been suggested as neutron sources [33]. While probably not a problem of the same magnitude as others previously discussed, shielding will be another engineering issue that needs to be addressed.

XII. COST

The ion production and acceleration part, which the laser technology challenges, comprises—depending on the number of treatment rooms—10%–20% of the whole floor plan and cost of a proton facility [19,34]. A cyclotron for proton-therapy costs, currently, less than 10×10^6 Euros. This is similar to the price quoted for a ''compact'' petawatt laser [35]. However, the cyclotron operates at only 200 kW, serves 3–5 treatment rooms, and lasts at least 30 years [19,36]. This clearly limits cost as a major argument in favor of laser-produced proton beams [5,11].

Reliability of the technology is preferred over prime design with a high degree of innovation. Ease of operation and fault tolerance are wanted. One example to illustrate the attitude might be the application of superconducting magnets. Despite the fact that weight and size could be saved, this technology is only applied by one of the six major manufacturers of IBT facilities.

Factors such as high beam availability ($\geq 95\%$ of the time, ≥ 12 h/d, 6 d/wk 48 wk/yr), infrequent, short maintenance periods, and long lifetime of the equipment do not only influence patient trust and acceptance. They are essential for the amortization rate of the facility [19]. It is hard to imagine how they could be mastered within the next years, given the fact that the laser generation to produce a therapeutic beam has not been put into practice.

XIII. CONCLUSIONS

The most important idea to be kept in mind is that providing a source of 200 or 250 MeV protons is not sufficient to make a successful IBT system. The interface between the accelerator and the patient—the hardware and software that effectively convert the beam from the accelerator into a radiation field suitable for therapy—are of paramount importance.

The beam-delivery systems developed for the present-day IBT configurations require incident particle beams that have well-defined energy, very narrow energy spread, and are tightly focused. These beam properties are not at all what is found in particles accelerated by laser pulses, and we have indicated that these accelerated protons cannot be easily interfaced with the existing beam-delivery systems.

In addition to having to develop an entirely new technology for effective beam delivery and dose conformation, the following challenges must be faced by the laser community: (i) verifying scaling laws for proton energy with laser power, (ii) improving proton flux by at least an order of magnitude, (iii) improving shot-to-shot reproducibility to the few-percent level, (iv) development of suitable dose-monitoring devices, (v) development of techniques for accurate dose control and cutoff, and (vi) addressing quality-assurance and patient-safety aspects. This is not to say that one should not work towards solving these tremendous problems! After all, it was realized over 100 years ago that orthovoltage x rays could be used for treating malignancies, but it took many decades—plus the development of a number of enabling technologies—before the concept became an effective medical technique. The developments necessary for effective implementation of laser-accelerated protons will possibly occur, but not tomorrow, nor in the next few years. This technology will not be able to replace conventional accelerators as an effective tool in IBT anytime soon.

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