

Chapter 1

Lasers Offer New Tools to Radiobiology and Radiotherapy

Antonio Giulietti and Toshiki Tajima

Abstract Multidisciplinary contributions of scientists actively operating in frontier laser science, radiation biology, tumor therapy, dosimetry and radiation safety provide a wide description of the status and perspectives of a primary field for human health care, in view of the emerging novel technology providing laser-driven sources of ionizing radiation.

1.1 Introduction

Though the rate of survivals increases regularly year by year, cancer is still the first cause of death everywhere. The number of *new* cases of cancer in the world is estimated to have been about 14 millions in the year 2012, with an expectation of more than 20 millions in 2020 [1]. About 50 % of cases are treated with radiation therapies, possibly in combination with surgery and/or chemotherapy, with an emerging problem for the access of low- and middle-income countries (LMIC) to radiation therapy [2].

Among these treatments, more than 90 % use RF-driven linear accelerators of electrons (RF-Linac). Other techniques include internal radiation (brachytherapy) and proton-ion beams (hadrotherapy). In most cases electrons delivered by a RF-linac are not used directly on the tumor but converted into photons (hard X-rays) by bremsstrahlung through a suitable target. In some case electrons are used directly, either to cure superficial tumors or in the Intra-Operative Radiation Therapy (IORT) which can be applied during surgical operation of a tumor [3, 4].

A. Giulietti (✉)

Istituto Nazionale di Ottica, Consiglio Nazionale delle Ricerche, Pisa, Italy
e-mail: antonio.giulietti@ino.it

T. Tajima

Department of Physics and Astronomy, University of California at Irvine,
Irvine, CA, USA
e-mail: ttajima@uci.edu

Radiation therapy techniques evolve and progress continuously and so do accelerators and dose delivering devices, which share a global market of about \$ 4 billions, growing at an annual rate exceeding 5 % [5]. Most of the progress involves precision in tumor targeting, multi-beam irradiation, reduction of damage on healthy tissues and critical organs, fractionation of dose delivering for a more effective cure [6]. Among these novel techniques and protocols of treatment, particularly effective appears the so-called Cyberknife. This technique uses a multitude of small beams which creates a large dose gradient resulting in the delivery of high dose to the tumor while minimizing the dose to adjacent healthy tissues [7]. This fast evolving scenario is the moving benchmark for the progress of the laser-based accelerators in order to become appealing towards clinical uses.

Basically, requested electron kinetic energy ranges from 4 to 25 MeV, but rarely energy above 15 MeV is used. Required dose/rate usually ranges from 1 to 10 Gy/min. These two ranges of performances are presently well fulfilled by plasma accelerators driven by ultrashort laser pulses of “moderate” peak power, i.e. tens of TW, operating within high efficiency laser-plasma interaction regimes at a pulse repetition rate of the order of tens of Hz [8]. However further work has to be done on laser acceleration in order to reach the clinical standard in terms of the electron output stability and reproducibility.

Several tasks have to be afforded before proceeding to a technical design of a laser-driven linac prototype for clinical tests. A first task is the optimization of both laser and gas-jet (or other possible targets) as well as their coupling (involving mechanical stability and optical design). Another task is the energy control of the electron bunch to provide different electron energies on clinical demand. These goals would require a complex scientific and technological investigation addressed to both the laser system, in order to make it as stable, simple and easy to use as possible and to the physics of the acceleration process, in order to get the highest possible efficiency, stability and output control [9].

We may nevertheless try and list some of the expected advantages of future Laser-linac’s for clinical uses. Laser technology strongly reduces size and complexity of the acceleration section (Mini-linac) of the device; it also totally decouples the “driver” from the acceleration section: we can imagine a single high power laser plant in a dedicated hospital room (with no need for radioprotection) which delivers pulses to a number of accelerators located in several treatment or operating rooms, suitably radioprotected. Laser managing and maintenance can proceed independently from the managing and maintenance of the Mini-linac’s. Each Mini-linac could be easily translated and rotated according to the given radiotherapy plan. Current studies could prove that the extreme dose-rate per pulse delivered by the Laser-linac would reduce the total dose for a therapeutical effect. This latter of course would be a major advantage of laser-driven radiotherapy.

The original idea of Laser Wake-Field Acceleration [10] and the advent of the decisive CPA laser technology [11] originated one of the most appealing scientific case of the last decades. Since then, a number of schemes for laser driven acceleration of electrons in plasmas have been proposed and studied, some of which were successfully tested. New experimental records have been reported in the

recent literature, in terms of the maximum electron energy achieved, the minimum energy spread, as well as maximum collimation, stability, and so on. These records are in general obtained with lasers of outstanding performances and/or with very sophisticated methods hardly applicable for practical uses. On the other hand, many labs are intensively working on scientific and technological innovations aimed at demonstrating that reliable laser-based devices can be built which are able to produce electron beams fulfilling requirements of specific applications. A major task is addressed to the possible clinical use of electron Laser linacs and their potential advantages with respect to the existing RF-linacs operating today for millions of daily hospital treatments in the world.

This is the context in which the exciting progress of laser-driven electron acceleration try to make this technique competitive with existing RF-based devices involved in 90 % of tumor treatments with radiation therapy. It has to be said however that Hadrotherapy, presently limited to a few percent of global treatments, is by far the most desirable way for the future to treat tumors with ionizing radiation. This is due to the peculiar character of energy deposition of hadrons in a medium. Figure 1.1 clearly shows that, treating a tumor at 15 cm depth, monoenergetic protons and Carbon ions of suitable kinetic energy deliver most of the dose in a thin layer (Bragg peak) around the tumor site, while monochromatic gamma rays (usually generated by bremsstrahlung of electrons) leave a lot of energy inside healthy tissues, before and after the tumor, with possible damages on these latter tissues.

It has to be said, this drawback for electron-based clinical devices has been strongly reduced with modern configurations allowing multi-beam irradiations at different angles [6, 7]. Nevertheless, hadrotherapy still remains the primary option for the future of radiotherapy, 70 years after its first conceptual proposition [12] followed by pioneering experimental tests [13]. Since then, hadron therapy was

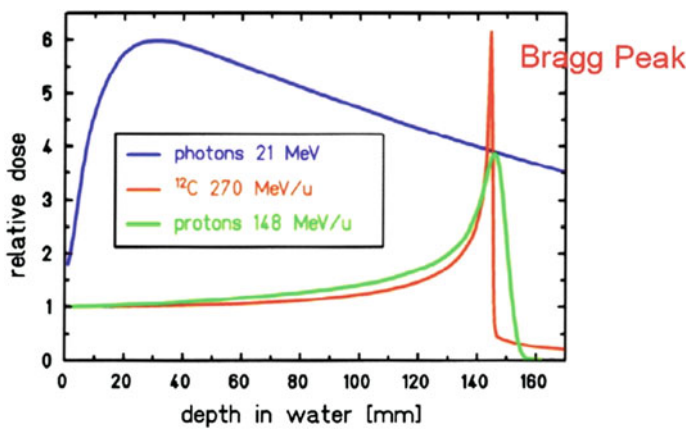


Fig. 1.1 Relative dose deposition versus depth in water for three kinds of ionizing agents, each one with a specific energy

occasionally performed inside accelerator facilities devoted to high energy physics, until the opening (1990) of a first clinical center equipped with a proton accelerator facility at Loma Linda Hospital in California (USA). In the last decades both the number of centers and the number of treated patients grew almost exponentially worldwide as shown in Fig. 1.2 [14]. More than 137,000 patients were treated with this therapy worldwide from beginning up to 2014, including 15,000 in 2014, 86 % of which were treated with protons and 14 % with carbon ions and with other particles.

Though the total number of treatments is still a small fraction of the total number of radiation treatments, this impressive growth demanded a huge capital investment which could be afforded only by the most rich countries. In fact, size and cost (both for construction and maintenance) of such facilities are presently major drawbacks for a wider diffusion of hadrotherapy. RF-based ion accelerators have faced an impressive progress, mostly in the synchrotron configuration [15] but typical acceleration gradients still remain of the order of 1 MeV/m, so that the typical diameter of an accelerator ring is several tens of meters for energies of clinical interest, namely $E \approx 100\text{--}400$ MeV/u, with severe costs involved [16]. Additional high costs and large spaces are requested by the very heavy gantry systems necessary to guide the particle beam onto the patient body from the right direction(s) and focus it with a millimeter precision [17].

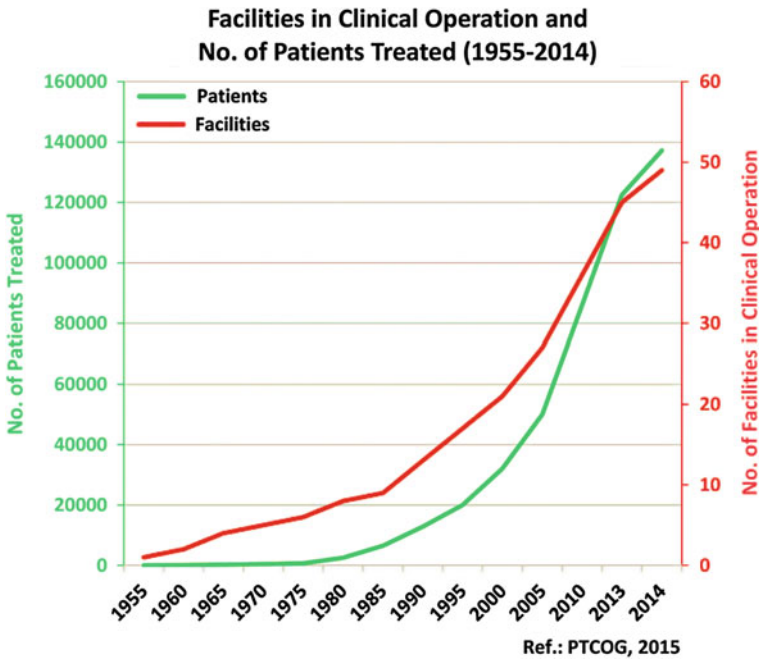


Fig. 1.2 Growth of hadrotherapy in treatment centers and treated patients worldwide (from [14])

With such a strong motivation, research on laser-based proton acceleration has been considerably supported in the last decade, mostly in the direction of achieving the challenging performances requested by the clinical standards. A usable device for cancer therapy needs to produce 200–250 MeV protons and/or 400–450 MeV/u carbon ions. In order to really profit of the Bragg peak, no more than 1 % energy bandwidth is requested. Further, to release a dose of therapeutic interest in a reasonable time, more than 10^{10} particle/s have to reach the tissue under treatment. None of these performances has been achieved so far with laser techniques. Some of them seem still hard to achieve with existing lasers or even with the next generation lasers, at least in a configuration practically usable in a hospital context. Nevertheless, the impressive crop of knowledge [18], the preliminary successful biological tests already performed [19] and some exciting new ideas [20] strongly encourage laser community in carrying on towards this challenging task.

Laser driven electron acceleration via excitation of plasma waves acts on free electrons already available in a plasma. In general the primary interaction of the laser field is with electrons (either bound or free), while action on massive particles (protons and ions) needs the intermediate role of electrons. For this reason, though evidence of the effect of the laser field on the ion velocity was found as early as high power lasers entered the laboratory, the first relevant effects on ion acceleration were observed, in the fusion research context, with powerful CO₂ lasers [21, 22]. These latter in fact, due to their large wavelength (10- μ m) can induce huge electron quiver velocities on plasma electrons.

Historically, ion acceleration in plasmas was proposed before the invention of optical lasers, as early as 1956 [23] and initially tested with electrons propagating in plasmas. Apart from initial observations related to fusion studies with infrared CO₂ lasers cited above, the laser driven ion acceleration studies with optical lasers could really start only after some decisive breakthrough towards high peak power lasers, like mode-locking (ML) for picosecond pulses and chirped pulse amplification (CPA) for femtosecond pulses [11]. About 1-MeV ions were produced in the early Nineties with picosecond laser pulses [24]. Since then, an impressive progress towards higher kinetic energies was continuously driven by both innovation in laser technology and better comprehension of the complex physics involved in the ion acceleration processes. Several proposals raised for a variety of schemes of laser-matter interaction at ultra-high (ultra-relativistic) intensities able to drive protons and light ions to near-relativistic energies. Most of them can be attributed either to *target normal sheath acceleration* (TNSA) or *radiation pressure dominated acceleration* (RPDA). This matter is deeply discussed by Borghesi and Macchi in the Chap. 10.

In a general view, considering the present state of the art, we can say that laser-driven acceleration to kinetic energies suitable for radiotherapy of cancer is well consolidated in the case of electrons and bremsstrahlung photons (with bunches delivering the requested dose). Effort is being invested towards achievement of corresponding energies for protons and light ions. Time for technological and commercial alternative with existing Hospital electron-Linac's as well as with huge plants already operating hadron therapy, may not be so far. In the case of electrons

most of the work to be still done, in order to achieve clinical standards, has to address the control of the electron energy, as well as stability and reliability of the laser-linac. In the case of protons and light ions the work to be done still includes the identification of an acceleration scheme able to produce particles of suitable energy (and energy spread) in bunches delivering the right dose.

However, there is a major scientific issue which has to be addressed from now, concerning potential radiobiological effects of the extremely different duration of bunches produced by laser with respect to bunches produced by conventional accelerators. A factor exceeding 1,000,000 is involved, from μs to sub-ps timescale. The ultrashort duration of laser-produced particle bunches may involve unexpected consequences for cancer therapy. In fact, it is not known if delivering the same dose with particles of the same kinetic energy but at much higher instantaneous dose-rate may lead to a different tissutal effects with possible consequences on therapeutic strategy and protocols [25]. From the physical point of view we can expect that the extreme particle density we can produce in a bunch with laser acceleration could behave “collectively” and/or lead to non-linear effects (see Sect. 11.4 of Chap. 11) which cannot be described by the usual single-particle Monte Carlo simulation. In other words it is possible that each ultradense bunch of electrons could produce not only the statistic sum of the effects of each low-LET particle but also some high-LET effect due to the total charge involved. If this would be true, the biological action could not only concern DNA but also some structural cellular feature, like membrane. This major issue, in turn, calls for a dedicated research on radiobiological effects to be performed with the ultrashort particle bunches produced by laser technology. It is evident that such a research also has a high conceptual value since it enables, for the first time, the investigation of very early processes occurring in the timescales of physical, chemical, biological responses of the living matter to ionizing radiation [26]. Investigation of very early effects arising from ultrashort ionizing pulses at nanometric scale become possible in a framework of advanced *femtochemistry*. This opportunity move also the interest of biologists, aimed at improving the “OMIC” approach to radiation therapy [27]. It should be pointed out that the use of laser in combination of an electron beam is capable of creating collimated energy-specific (and energy-tunable) X-rays and γ -rays via the laser Compton scattering process. Such photons can be a valuable source for radiation oncology. For example, this can yield valuable radioisotopes useful for specific purposes in radiobiology and oncology [28].

1.2 Dealing with Protons and Ions

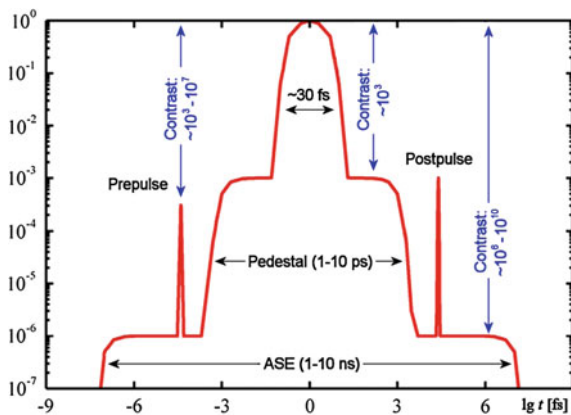
A high power laser primarily acts with its e.m. field on electrons (first bound, then free after ionization), while action on massive particles (protons and ions) needs the intermediate role of these electrons. This scenario has been described in many works after the advent of powerful laser systems and has been recently reviewed within the correct theoretical background by Mulser and Bauer [29]. More recent

review papers specifically devoted to laser-driven ion acceleration includes [30] and [31], this latter more addressed to applications. The reader can find an updated discussion of the main acceleration mechanisms, including *Target Normal Sheath Acceleration*, *Radiation pressure acceleration* and *Collisionless shock acceleration*, in the Sect. 10.2 of Chap. 10.

Apart for some “exotic” targets or sophisticated configurations reviewed in [30, 31], proton spectra produced by TNSA show a broad, thermal-like energy spectrum. This feature risks to vanish the advantages of the Bragg peak in deep energy deposition, which is the strongest motivation for hadron therapy. Most of the energy broadening in the TNSA acceleration is due to the initial distribution of protons in a wide region where the accelerating field varies considerably. An effort at designing special targets (e.g. with small dots of proton-rich material on surface or “grating targets” [32]) is currently in progress with a partial but encouraging success. At the same time several kind of passive filters able to reduce the outcoming proton spectrum are tested. It has to be considered, however, that any kind of passive particle filtering will introduce an additive radioactivation trouble in a clinical context. Novel simulations of acceleration with single-cycle laser pulses, based on a very recent idea of realizing single-cycle laser emission at high power [33], are discussed in Sect. 13.4 of Chap. 13.

In most of the laser-based ion acceleration schemes a crucial role is played by the *laser pulse contrast*, more exactly by the ratio between the main pulse peak power and the power associated with the light emitted by the laser chain *before* the main pulse itself. In Fig. 1.3 the emitted power versus time is sketched in a log-log diagram. Though all the early emission is often indicated as *prepulse*, the actual prepulse (left hand peak in Fig. 1.3) is an ultrashort pulse, similar to the main pulse but much weaker, leaking from the electro-optical shutter out of the oscillator. This prepulse usually carries a negligible amount of energy (and power). More dangerous is the *amplified spontaneous emission* (ASE), which lasts typically a few nanosecond and then carries a considerable amount of energy, comparable with the main pulse energy if the contrast is worse than 10^6 . In most of the previous

Fig. 1.3 Time evolution of parasitic laser emission before and after the main pulse (image from [35])



experiments on laser-driven proton acceleration this *ns-contrast* had to be increased above 10^9 , with several means, including the “plasma mirror” technique [34].

Early emission a few picosecond before the main pulse (*ps-pedestal*) involves the *ps-contrast* which is usually 3–4 orders of magnitude worse than the ASE-contrast, but carries much less energy. It can be nevertheless dangerous as well. It can be reduced only assuring high quality and accuracy in the optical compression of the stretched amplified pulse at the end of the laser chain. A critical feature of the pre-pulse problem is that most of the undesired effects depend on the absolute value of the pre-pulse energy and power and not from the value of the contrast. In other words, increasing the laser power, as requested by most of the advanced schemes of acceleration, the contrast has to be increased correspondingly. This technical point deserves a special attention for the future of laser-driven ion accelerators.

It has been clear for a long time that, differently from electrons, proton sources driven by laser need not only high pulse peak intensity but also high energy per pulse. A pioneering experiment from Lawrence Livermore National Laboratory, demonstrated high current proton beams of several tens of MeV's [36] with PW laser pulses whose high contrast was assured by a plasma-mirror technique [34]. Preliminary investigations were performed in many laboratories with femtosecond and picosecond pulses of different power. These investigations were quite useful to assess the validity of various schemes achievable at the available laser fluence but they also evidenced that for getting kinetic energy and mean proton current suitable for clinical application, a general laser upgrading was necessary. Further, a decisive progress of laser technology towards higher peak power, higher contrast (see above), higher repetition rate has to be faced.

Though protons produced with laser-plasma techniques are still far from clinical requirements, they are currently used for preliminary tests on biological samples in order to assess their capability as ionizing agent, also considering the ultra-short duration of the laser-produced particle bunches, compared with the ones delivered by RF-based machines. Relatively low kinetic energy, broad energy spectrum and large divergence of the beams do not prevent possibility of such investigations.

Taking into account their high-LET (linear energy transfer), a few MeV protons have been compared, in terms of relative biological effectiveness (RBE), with both RF-accelerated protons and standard X-ray sources. Yogo et al. have first demonstrated breaking of DNA in human cancerous cells with laser-accelerated protons [37], then measured their RBE [38] A relevant feature of laser-produced proton bunches lies on their outstanding instantaneous dose rate, due to their duration of about 1 picosecond, more than one million times shorter than RF-produced pulses. Dose rate as high as 10^9 Gy/s have been obtained and tested on biological samples [39]. A more extended overview on this kind of experimental investigations can be found in Sect. 11.3 of Chap. 11.

Another interesting biological application of energetic protons and ions produced with laser techniques is radiography [40]. In fact, the unique properties of protons, multicharged ions and electron beams generated by high-intensity laser-matter interactions, particularly in terms of spatial quality and temporal

duration, have opened up a totally new area of high-resolution radiography. Laser-driven radiographic sources obtained by irradiation of clustered gases were proved to be particularly effective, leading to large-field high-contrast images with 1 μm spatial resolution [41].

1.3 Dealing with Electrons and Photons

If we limit our consideration to radiotherapy, present table-top laser driven electron accelerators can be already considered as candidate. In fact, for this medical application, most of the requirements usually asked to electron bunches are practically achieved. Small divergence, monochromaticity, pointing stability, etc. are requested at a moderate level, while the main effort has to be devoted to efficiency, stability and reliability of the process in order to provide clinically acceptable devices.

As far as the efficiency is concerned, in an experiment performed at CEA-Saclay (France) a regime of electron acceleration at high efficiency was found, using a 10 TW laser and a supersonic jet of Helium [8]. This *table-top* accelerator delivered high-charge (nC), reproducible, fairly collimated, and quasimonochromatic electron bunches, with peak energy in the range 10–45 MeV. In Fig. 1.4 a typical cross section of the relativistic electron beam at 25 MeV is shown, after de-convolution of experimental data from the SHEEBA radiochromic film stack device [42].

3D particle-in-cell simulation performed with the numerical code CALDER [43] reveals that the unprecedented efficiency of this accelerator was due to the achievement of a physical regime in which multiple electron bunches are accelerated in the gas-jet plasma during the action of each laser shot.

With this experiment, laser driven electron acceleration approached the stage of suitability for medical uses, in particular for Intra-Operative Radiation Therapy (IORT) of tumors [3, 4]. Comparison of the main parameters of electron bunches

Fig. 1.4 25-MeV electron beam cross section (Giulietti et al. [8])

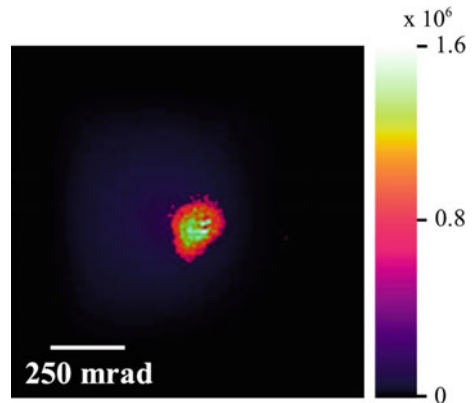


Table 1.1 Comparison between commercial RF-linac's and experimental laser-linac pulse (table from [34])

Linac	IORT-NOVAC7	LIAC	Laser-linac (experimental)
Company	(SORDINA SpA)	(Info & Tech Srl)	(CEA-Saclay)
Max electron energy (MeV)	10	12	45
Available energies (MeV)	3, 5, 7, 9	4, 6, 9, 12	5–45
Peak current	1.5 mA	1.5 mA	>1.6 KA
Bunch duration	4	1.2 μ s	<1 ps
Bunch charge (nC)	6	1.8	1.6
Repetition rate (Hz)	5	5–20	10
Mean current	30 nA @5 Hz	18 nA @10 Hz	16 nA @10 Hz
Released en. in 1 min.	18 J @ 9 MeV	14 J @12 MeV	21 J @20 MeV

produced by a commercial RF Hospital accelerator for IORT treatment and those of the present laser driven accelerator is shown in the Table 1.1.

In the same experiment electron bunches of ≈ 40 MeV were converted, via bremsstrahlung in a tantalum foil, into gamma rays with a strong component in the range 10–20 MeV, which matches the Giant Dipole Resonance of nuclei. This gamma rays could in turn activate a foil of gold according to the nuclear reaction $^{197}\text{Au}(\gamma, n)^{196}\text{Au}$. The number of radioactive gold atoms produced in this way was measured [8]. This achievement opens the way to table-top laser-driven nuclear physics and production of radio-isotopes for medical uses. It is also noted that the laser Compton X-rays (and γ -rays) may be generated of laser off an electron beam, whose applications have been mentioned in [28].

As already said in the Introduction, in most cases electrons delivered by a RF-linac currently used in Hospitals, are not sent directly on the tumor but previously converted into photons (hard X-rays) by bremsstrahlung through a suitable target. Of course this is possible also for electrons of comparable energy currently produced in high-power laser labs. Laser-driven electron accelerators would be then ready for clinical uses provided a suitable stability, uniformity and reproducibility of the electron bunches will be reached [9].

Interestingly, such level of performances have been recently approached with sub-MeV electron bunches produced by a laser-plasma device [44]. This source delivers ultrashort bunches of electrons with kinetic energy around 300 keV, uniformly over a large solid angle. The device is presently setup for radiobiological tests covering a previously untested energy range. Each bunch combines high charge with short duration and sub-millimeter range into a record instantaneous dose rate, as high as 10^9 Gy/s. Both such a high dose rate and high level of Relative Biological Effectiveness, attached to sub-MeV electrons, make this source very attractive for radiobiological tests on thin samples of living cells.

Secondary sources of high-energy photons are another exciting by-product of laser-driven electron acceleration. They include the above mentioned bremsstrahlung sources and betatron sources originated during the laser wakefield process itself by the strong restoring forces moving electron bunches towards the laser propagation axis. Further, the electron beam produced by laser-driven acceleration can be sent to collide with another powerful laser pulse and produce energetic photons by Compton scattering [45, 46].

Generation of radiation via Thomson (Compton) scattering of a laser pulse by energetic counter-propagating electrons was initially proposed in 1963 [47, 48] as a quasi monochromatic and polarized photons source. With the development of ultra intense lasers the interest on this process has grown and the process is now being exploited as a bright source of energetic photons from UV to gamma-rays and atto-second sources in the full nonlinear regime. In view of medical application, tuneability of the X-ray photon energy may be an important option of an *all-optical* laser-based Thomson source. Recent experiments performed by Sarri et al. [49] and Liu et al. [50] obtained photons of several tens of MeV and opened a new phase of these studies.

We mentioned in the previous Section radiography performed with protons and ions. A similar technique can be used also with electron beams produced by laser-driven accelerators. This topic is treated in Sects. 13.5 and 13.6 of Chap. 13 where several preliminary results are discussed, leading to high resolution imaging of material and biological samples. The laser-driven electron sources included interaction with both ordinary and clustered gas jets [51, 52].

As we saw so far, the present status of laser-driven electron acceleration already allow to (i) consider the feasibility of clinical devices; (ii) to perform outstanding experiments in order to assess further, more advanced applications. Nevertheless, we can't ignore the continuous progress of the acceleration methods and techniques that could lead in short period of time to unexpected opportunities also of biomedical interest. The possible biomedical impact of laser-generated multi-GeV electron beams is deeply discussed in the Chap. 6 of this Volume [53] together with a wide overview of the basic concept [54] and emerging results making possible to design and test novel configurations including multi-stage accelerators [55].

In this context of advanced researches, an increasing interest has been raised by the *ionization induced* electron *injection* in laser wakefield acceleration [56]. Compared with other electron injection schemes [57] for laser wakefield acceleration, this scheme shows the merits of relatively simple operation and controllable final beam quality. In the *single-color* laser ionization injection scheme, quasi-monoenergetic electron acceleration is possible through the control of laser self-focusing. In this way the effective injection length can be controlled within a hundred micrometers range and the absolute energy spread of the beam can be controlled within tens of MeV. In the *two-color* laser ionization injection scheme, the effective injection length can be further reduced to tens of micrometers length, and the absolute energy spread of the electrons can be reduced to a few MeV, i.e. the relative energy spread can be less than 0.5 %. A further interesting result is the

generation of multi-color electron bunches by use of two-color lasers [58]. These electrons can be used for multi-color X-ray generation through laser beam Thomson scattering.

1.4 Dosimetry and Safety

Several primary issues have to be addressed before transferring laser-driven particle beams from laboratory to clinic, including suitable and reliable dosimetric methods and ad hoc protocols for radiation safety. Chapter 9 is actually devoted to dosimetry of laser-driven electron beams for radiobiology and medicine [59]. Both absolute and relative dosimetry are considered, in the framework of international protocols [60]. Several existing devices are considered and discussed, including radiochromic foils, ionization chambers and Faraday cups. Novel concepts for ad hoc detectors are presented, including a recently published, innovative Faraday cup [61]. The response of each device to the very high dose rates delivered by laser-driven accelerators needs to be carefully investigated.

Section 9.3 of Chap. 9 is devoted to dosimetric simulations with Monte Carlo methods, in particular with the GEANT4 toolkit, widely used for medical physics. Simulations have been adapted to the peculiar geometry of laser-driven acceleration and can produce realistic evaluations of dose distribution, as well as duration and spectrum, of the particle bunch at the source, at the vacuum/air interface, and finally on the biological specimen.

Dosimetric issues concerning protons and ions accelerated with laser techniques are also treated in Chaps. 10 and 11 [18, 19]. In particular, in Sect. 10.3 of Chap. 10 reports dose measurements performed with devoted dosimetric techniques [62]. In Sect. 11.3 of Chap. 11 the proton dose is estimated from the measured proton number and energy spectrum per bunch using a Monte-Carlo simulation with the TRIM code. TRIM is a group of programs which calculate the stopping power and range of ions (10 eV–2 GeV/u) in matter using a quantum mechanical treatment of ion-atom collisions. Note that the TRIM code accurately calculates the range and energy loss of ions having energies below the region where Bethe-Bloch equation is adopted. The stopping power table used in this work was SRIM2008 [63].

One of the primary issues to be considered, while thinking to transfer laser-driven acceleration technology in a clinical context, is radiological safety. This would be not exactly the same set of problems and protocols as for conventional accelerators delivering a well defined type of particle with an almost monoenergetic spectrum. We are dealing with a complex of radiological products delivered by laser interaction, at a given but changeable intensity, with a variety of materials acting as accelerating media. Of course this kind of problems have already considered and studied by managing high-power laser facilities devoted to laser-matter interactions and more specifically to particle acceleration. Activation of experimental targets is often an experimental goal but activation of diagnostics, vacuum

chambers and the facility beyond needs to be considered. Experimenters, technicians and other facility personnel will come into contact with this equipment often within minutes of a shot or short series and their safety is the central concern to any facility or program manager. For a medical facility the safety of the patient is paramount, i.e. ensuring the radiation interacts as intended whilst minimizing doses from any secondary radiations and considering all other hazards [64]. To this fundamental and somehow challenging topic is deeply analyzed in Chap. 5.

1.5 How Far We Are

A complex culture made by many multidisciplinary contributions is growing up from the original scientific case of laser-driven particle acceleration in order to make it useful and usable for biology and medicine. This volume may provide a partial but significant insight on this new, fast progressing scientific and technological reality.

How far we are from prototyping novel classes of laser-based accelerators able to get the huge market of radiotherapy is difficult to understand. For sure a new class of radiobiological investigations is running. Some of them are mostly tests on the RBE of the laser-produced particle bunches and are very important to assess the validity of the laser technologies. Some others try to explore the very early effects of the ionizing radiation on temporal and spatial scale not attainable before. These latter can improve significantly the basic knowledge to be transferred into future, less aggressive models of radiotherapy.

For laser-driven electron acceleration, many scientific issues of the physics of laser electron acceleration have been already addressed [65], while the technology of intense laser needs to be improved in such elements as in the repetition rate and efficiency. The recently invented fiber laser technology [33] specifically targeted and proposed remedies on these issues in a novel fashion. As to laser ion acceleration, as mentioned in some of the chapters of this volume, it is important to make the bucket that traps ions move in a fashion of the adiabatic acceleration [20] to be more efficacious and of higher quality for the ion beam. There are multiple of directions to improve on this point. Some of these need to be further developed to see their full potential, consequences, and impacts in the future. The breadth of spectrum of these attempts is encouraging.

Acknowledgments We are delighted by and appreciative of all the authors who contributed to this volume. These efforts make our paper writing so much easier. This work was in part supported by the Norman Rostoker Fund.

References

1. IARC, Cancer fact sheets. Globocan, <http://globocan.iarc.fr/>
2. D. Rodin et al., *Lancet Oncol.* **15**, 378 (2014)
3. U. Veronesi et al., *Ann. Oncol.* **12**, 997 (2001)
4. A.S. Beddar et al., *Med. Phys.* **33**, 1476 (2006)
5. <http://www.businesswire.com/news/home/20140313005577/en/Research-Markets-External-Beam-Radiation-Therapy-Devices>
6. R. Baskar et al., *Int. J. Med. Sci.* **9**, 193 (2012)
7. R. Mouttet-Audouard, T. Lacornerie, and E. Lartigau, Chapter 3 of this volume (2016)
8. A. Giulietti et al., *Phys. Rev. Lett.* **101**, 105002 (2008)
9. F. Baffigi et al., The LEARC concept: laser-driven electron accelerator for radiotherapy of cancer, INO-CNR internal report (2014). Available at: www.ilil.ino.it
10. T. Tajima, J. Dawson, *Phys. Rev. Lett.* **43**, 267 (1979)
11. D. Strickland, G. Mourou, *Opt. Commun.* **56**, 219 (1985)
12. R.R. Wilson, *Radiology* **47**, 487 (1946)
13. J. Lawrence, *Cancer* **10**, 795 (1957)
14. M. Jermann, *Int. J. Particle Ther.* **2**, 50 (2015)
15. S. Sawada, *Nucl. Phys. A* **834**, 701 (2010)
16. M. Goitein, A.J. Lomax, E.S. Pedroni, *Phys. Today* **55**, 45 (2012)
17. M. Schippers, Beam delivery system for particle therapy, in *Proton and Ion Carbon Therapy*, ed. by C.-M. Charlie Ma, Tony Lomax (CRC Press, Boca Raton, FL, 2013), p 43
18. M. Borghesi, A. Macchi, Chapter 10 of this volume (2016)
19. A. Yogo, Chapter 11 of this volume (2016)
20. T. Tajima, Chapter 13 of this volume (2016)
21. W. Friedhorsky, D. Lieber, R. Day, D. Gerke, *Phys. Rev. Lett.* **47**, 1661 (1981)
22. D.M. Villeneuve, G.D. Enright, M.C. Richardson, *Phys. Rev. A* **27**, 2656 (1983)
23. V. I. Veksler, *Proceedings CERN Symposium on High Energy Accelerators and Pion Physics*, vol. 1 (Geneva, Switzerland, 1956), p 80
24. A.P. Fews, P.A. Norreys, F.N. Beg, A.R. Bell, A.R. Dangor, C.N. Danson, P. Lee, S.J. Rose, *Phys. Rev. Lett.* **73**, 1801 (1994)
25. S.S. Bulanov et al., *Med. Phys.* **35**, 1770 (2008)
26. Y.A. Gauduel, Chapter 2 of this volume (2016)
27. L. Minafra, V. Bravata, F. P. Cammarata, G. I. Forte, Chapter 4 of this volume (2016)
28. D. Habs, T. Tajima, U. Koester, Laser-driven radiation therapy, in *Current Cancer Treatment: Novel Beyond Conventional Approaches*, Chap. 10, ed. by O. Ozdemir (Intech, Rijeka, 2011), p. 199. ISBN 978-953-307-397-2. doi:10.5772/24190). <http://www.intechopen.com/books/show/title/current-cancer-treatment-novel-beyond-conventional-approaches>
29. P. Mulser, D. Bauer, *High Power Laser-Matter Interaction*. Springer Tracts in Modern Physics, vol. 238 (Springer, New York, 2010)
30. A. Macchi, M. Borghesi, M. Passoni, *Rev. Mod. Phys.* **85**, 751 (2013)
31. H. Daido, M. Nishiuchi, A.S. Pirozhkov, *Rep. Prog. Phys.* **75**, 056401 (2012)
32. T. Ceccotti et al., *Phys. Rev. Lett.* **111**, 18501 (2013)
33. G. Mourou, B. Brocklesby, T. Tajima, J. Limpert, *Nat. Photonics* **7**, 258 (2013)
34. M.D. Perry et al., *Opt. Lett.* **24**, 160 (1999)
35. A. Giulietti et al., Laser-plasma particle sources for biology and medicine, in *Progress in Ultrafast Intense Laser Science XII*, ed. by K. Yamanouchi et al., Springer Series in Chemical Physics, vol. 112 (Springer International Publication, Switzerland, 2015). doi 10.1007/978-3-319-23657-5_8
36. R.A. Snavely et al., *Phys. Rev. Lett.* **85**, 2945 (2000)
37. A. Yogo et al., *Appl. Phys. Lett.* **94**, 181502 (2009)
38. A. Yogo et al., *Appl. Phys. Lett.* **98**, 053701 (2011)
39. D. Doria et al., *AIP Advances* **2**, 011209 (2012)
40. A.Ya. Faenov, T.A. Pikuz, R. Kodama, Chapter 12 of this volume (2016)

41. A.Ya. Faenov, T.A. Pikuz, Y. Fukuda et al., *Appl. Phys. Lett.* **95**, 101107 (2009)
42. M. Galimberti et al., *Rev. Sci. Instrum.* **76**, 053303 (2005)
43. E. Lefebvre et al., *Nucl. Fusion* **43**, 629 (2003)
44. L. Labate et al., LESM: a laser-driven sub-MeV electron source delivering ultra-high dose rate on thin biological samples. *J. Phys. D Appl. Phys.* (2016)
45. L.A. Gizzi, Chapter 8 of this volume (2016)
46. L.A. Gizzi et al., *IEEE Trans. Plasma Sci.* **39**, 2954 (2011)
47. R.H. Milburn, *Phys. Rev. Lett.* **10**, 75 (1963)
48. C. Bemporad, R.H. Milburn, N. Tanaka, M. Fotino, *Phys. Rev.* **138**, B1546 (1965)
49. G. Sarri et al., *Phys. Rev. Lett.* **113**, 224801 (2014)
50. C. Liu et al., *Opt. Lett.* **39**, 4132 (2014)
51. G.C. Bussolino et al., *J. Phys. D Appl. Phys.* **46**, 245501 (2013)
52. P. Koester et al., *Laser and particles beams* **33**, 331 (2015)
53. T.M. Jeong, J. Lee, Chapter 6 of this volume (2016)
54. W. Leemans, E. Esarey, *Phys. Today* **62**, 44 (2009)
55. H.T. Kim et al., *Phys. Rev. Lett.* **111**, 165002 (2013)
56. M. Chen, Z.-M. Shen, Chapter 7 of this volume (2016)
57. E. Esarey et al., *Phys. Rev. Lett.* **79**, 2682 (1997)
58. M. Zeng et al., *Phys. Rev. Lett.* **114**, 084801 (2015)
59. L. Labate, D. Lamia, G. Russo, Chapter 9 of this volume (2016)
60. International Atomic Energy Agency, *Absorbed Dose Determination in External Beam Radiotherapy: An International Code of Practice for Dosimetry Based on Standards of Absorbed Dose to Water*, IAEA Technical Reports Series no. 398—IAEA, Vienna (2000)
61. G.A. Cirrone et al., *Nucl. Instrum. Meth. Phys. Res. A* **796**, 99 (2015)
62. F. Fiorini et al., *Phys. Med. Biol.* **56**, 6969 (2011)
63. J.F. Ziegler, J.P. Biersack, M.D. Ziegler, *SRIM, the Stopping and Range of Ions in Matter*. SRIM Company (2008)
64. A. Simons, Chapter 5 of this volume (2016)
65. W. Leemans, W. Chou, M. Uesaka (eds.), *Beam Dynamics Newsletter*, vol. 56, (ICFA, Fermilab, 2011), p. 7

Laser-Driven Particle Acceleration Towards Radiobiology
and Medicine

Giulietti, A. (Ed.)

2016, XVIII, 320 p. 106 illus., 78 illus. in color.,

Hardcover

ISBN: 978-3-319-31561-4