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(draft white paper)
Towards micron-scale electron therapy at the tip of endoscopy – Source and delivery of fiber-optic based laser wakefield accelerator

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Abstract

The adoption of the fiber laser technology and the in-situ delivery ability of the electrons by this allows much smaller accelerators of electrons (so tiny that it can site in front of the cancer tissues) and more targeted therapies are considered, which allow much tinier and more accurate therapies realized. The concept of this new integration of the various novel technologies (such as the latest high density regime of the laser wakefield accelerators, currently developing fiber laser technologies, etc. allows this novel developments of radiotherapy of cancers. Furthermore, we suggest a future applications of such combination to the other diseases such as,……… ……… etc.

Part I. Motivation – applying laser wakefield acceleration in directed oncology treatment

Laser Wakefield Acceleration (LWFA) uses ultrashort, intense laser pulses to drive plasma wakefields, which can accelerate charged particles like electrons or protons to high energies over short distances. Proposed by Tajima and Dawson [1] in 1979, its realization was aided with the advent of Chirped Pulse Amplification [2] (CPA) in ultra-intense lasers which accelerate electrons to GeV energies on a scale of centimeters. This new way of particle acceleration by laser has been proven with cost and size advantages over conventional particle accelerators such as synchrotron and linear accelerators [3].

Conventional radiotherapy – external and areal treatment

Traditional radiotherapy uses high-energy X-rays, electrons, or proton beams to target and destroy cancer cells. Conventional particle accelerators based on radiofrequency electromagnetic technology are bulky and expensive. The innovation of laser wakefield acceleration (or simply laser acceleration) is a much more efficient technique of particle acceleration which has garnered attention for its potentials in various fields, including radiotherapy treatment [3].

In the often-used radiotherapy, the electron source is placed externally to patient's body. Electron energy of many MeV is required, because for penetrating every 1 cm of body tissue, up to 10 MeV of electron energy is needed. The accelerated electrons of tens or hundreds of MeV may be obtained by conventional accelerators based on radio-frequency technology or the new laser-driven acceleration.

Vector nanomedicine and brachytherapy

In overcoming collateral damage to patient's healthy tissue and organs from above radiotherapy, new medical treatment techniques were developed for radiation delivery in close proximity to treatment sites. In vector nanomedicine, nanoparticle vector delivers high-Z metal to cancer cells [4]. In Brachytherapy applicator tubes [5] are used to deliver radio-active source locally with the right amount of dose. One may read further from the references.

Proposed endoscopic "vector" treatment with LWFA

In light of a proximity oncology treatment, a collaboration of medical researchers and physicists proposed [5,6] an endoscopic or colonoscopic radiotherapy apparatus, i.e., to bring a small laser electron accelerator at the tip of the scope, adding the treatment capability to the normal functions of endoscopy. Electrons of 10 keV to 100 keV created at the tip of an endoscope can eradicate cancer cells exposed in front of the accelerator. The much lower energy electrons penetrate microbic thickness of cancer cells with direct irradiation instead of going through patient's body.

This compact, micro-scaled electron source for therapy is possible based on the guidance of LWFA theory, fiber laser and flexible light delivery technologies. Depicted in figure 1 of a concept schematic, laser pulses are brought in with a flexible channel, focused to a solid target of nanomaterial. Electron beam is generated and accelerated to 10 keV to 100 keV energies next to the treatment side and irradiates cancer cells. This makes a new type of radiotherapy out of the routine endoscopic or colonoscopic inspection procedure. Treatment is controlled with precise dose, thus not causing collateral damage that comes with conventional radiotherapy. Other advantages are discussed in Roa *et al* paper [5]. No radioactive materials under regulation are needed and there are cost advantages over conventional accelerators.

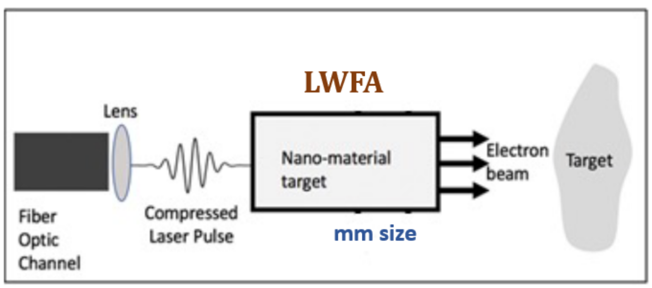

Figure 1.. Electron accelerator at the tip of an endoscope or colonoscope for targeted therapy after reference [5].

Efficient and effective laser electron acceleration in the range of 10 keV to 100 keV has been extensively studied recently by Barraza-Valdez *et al*. [7]. In the near-critical density regime, laser wakefield acceleration is most favorable with 30% energy efficiency that makes possible a tiny electron accelerator, which can be placed at the tip of endoscopes.

Part II of this paper provides a summary on theory of operation in the near-critical regime for the proposed endoscopic accelerator. In Part III and IV, recent innovations of ultrafast fiber lasers and flexible laser pulse delivery are reviewed. These are the ready technologies to be applied for the realization of the micron-scale electron accelerator.

Part II. Operating principle of micron-scale electron accelerator

Laser wakefield acceleration

Over the last few decades, LWFA has advanced to become an alternative form of particle acceleration by using high-intensity pulsed laser of 10^{18} W/cm^2 or greater to produce a 1000-fold higher acceleration gradient on the order of GeV/cm [1,3]. This alternative form of particle acceleration using lasers has the clear advantage of space and cost savings. Conventional GeV accelerators such as synchrotrons of large building size or linear accelerator scaled at hundreds of meters can now be made with plasma wakefield accelerator driven by petawatt-peak-power (10^{15} W) laser system that occupies laboratory space in comparison.

Such operation of LWFA in the high-energy domain is with laser intensity $a_0 > 1$ or 10^{18} W/cm^2. LWFA operates in the underdense gaseous regime with plasma density in the range of 10^{17}–10^{19}/cm^3 which is far away from the critical density (for a typical 1 μm laser, the critical density for the plasma is on the order of 10^{21}/cm^3). Performing in the underdense regime is necessary for obtaining long interacting length between the laser and the plasma to accelerate electrons to hundreds of MeV and GeV energy levels. Typical efficiency is 1% or lower.

Near-critical density, high-efficiency LWFA operation for endoscopic accelerator

Proposed endoscopic accelerator operates at lower electron energies from 10 keV to 100 keV as discussed in Part I. Recent studies show LWFA operating in the near-critical density regime can yield the necessary electron energy for therapeutic use at laser intensity as low as 10^{14} W/cm^2 [7,8]. Such laser intensity can be readily obtained from the relatively low-peak-power and compact lasers of gigawatt (GW) and sub-GW class. Ultrafast fiber laser systems, developed in technology and marketplace, deliver this level of performance. These systems can be packed in an instrument-sized box with turn-key operation, suitable for medical applications like the intended endoscopic accelerator.

Distinct and significant features of near-critical-density LFWA are clarified by particle-in-cell simulations and the results are summarized in the following figures [7,8].

When the plasma density approaches the near-critical density, laser pulse and plasma wakefield travel much slower than the speed of light, trapping more thermal electrons that are accelerated by the wakefield. As illustrated by the left chart in Figure 2, particle counts significantly increase when approaching critical density n_{crit}. Acceleration takes place in non-relativistic regime with relatively low laser intensity $a_0 << 1$. The chart on the right displays laser-to-electron conversion efficiency when plasma density increases towards the critical density. **Conversion efficiency is as high as 30%** at near-critical-density, compared to 1% or lower typically in the underdense regime.

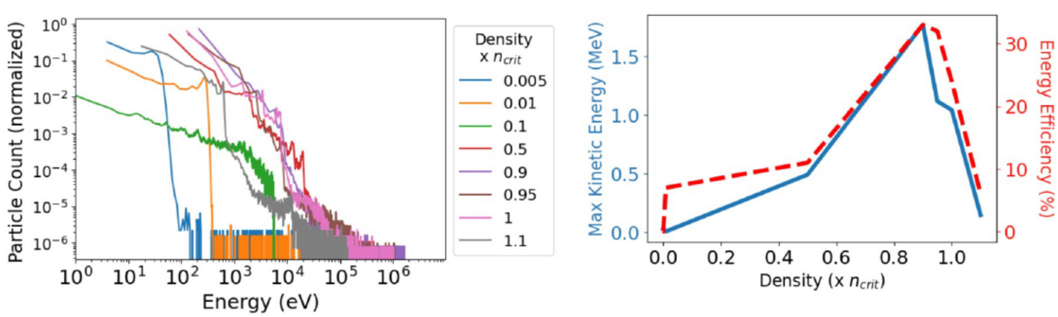

Figure 2. Electron energy spectra (left) and laser-electron conversion efficiency (right) with increasing plasma density towards the critical density, adopted from reference [7].

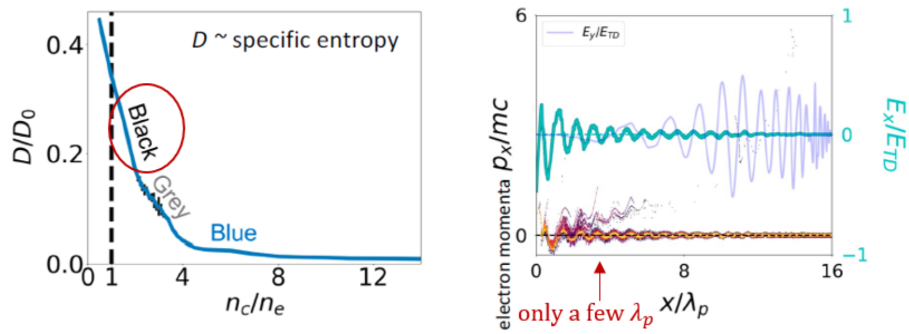

Figure 3. (Left) Regimes of plasma wakefields with various plasma density n_e with respect to critical density n_{crit}; (Right) Plots with electron momentum, space-charge field along the laser propagation direction. From reference [8].

In the left-hand-side chart in figure 3, the near-critical-density regime is signified by the black wave when the plasma density is increased from right to left (horizontal scale of plasma density is inversed and the dash line is the critical density). Black wave is an analogy from a tsunami wave approaching shore with low phase velocity as it traps objects. The right-hand-side chart displays electron momentum and wavefield magnitude along the laser propagation (and electron acceleration) path normalized to plasma wavelength. Acceleration occurs in **a few plasma wavelengths on the order of microns**. This infers that the accelerator medium can be of micron sizes.

Experimental Realization of Near-Critical Density LWFA

Theory of operation [8] at near-critical density is experimentally tested in KPSI very recently as shown in figure 4 [9]. High-density plasma is generated by ionizing glass capillary and electrons are accelerated by the wakefield. They measured electron energy over a range of laser intensity. Electrons energies greater than 50 keV are observed which results are in line with the simulations.

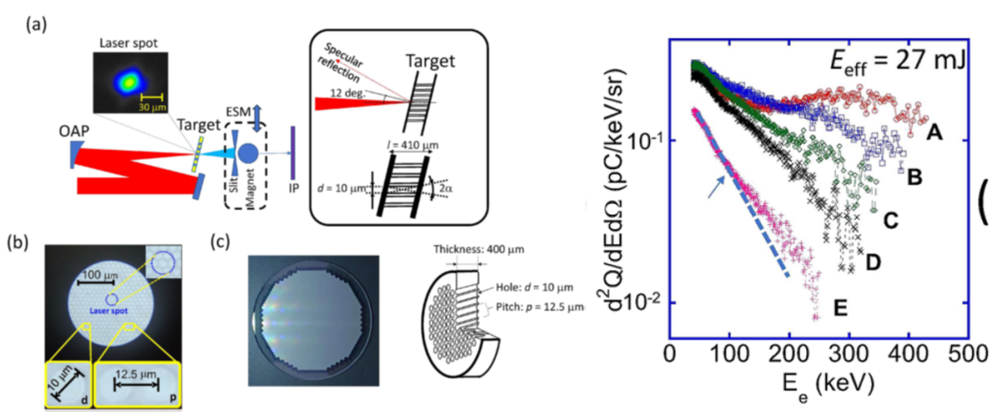

Figure 4. Near-critical density LWFA is experimentally verified. Charts are adopted from reference [8].

Carbon nanotubes as the solid target

As it is desirable to operate in the near-critical density regime with the typical 1-µm wavelength pulse laser, the respective critical density of the plasma is $10^{21}/cm^3$. This exceeds the usual gaseous plasma density. *Carbon nanotubes* (CNT and possibly other nanomaterials) offers design flexibility to dial in the critical density by tailoring its occupation ratio, such as the tube diameter [11]. An illustration is given in figure 5. In addition, CNT is solid material, a desired form of LWFA target for endoscopic operation [12] .

The physical size of laser accelerator with gaseous plasma (operating in the underdense regime) is already far smaller than that of conventional RF accelerators. The solid target with porous-like carbon nanotubes in the high-density LWFA further reduces the size of the laser accelerator. Discussed earlier, near-critical density operation takes micron length in plasma, therefore mounted target material can be made millimeters in size, to be placed at the tip of endoscopes.

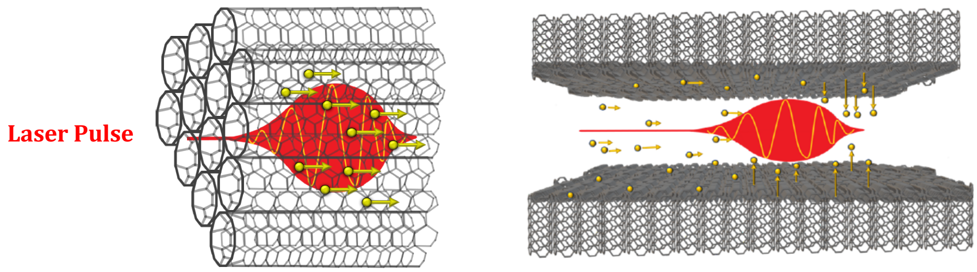

Figure 5. CNT's tube diameter can be flexibly produced to dial in critical density after reference [8] Laser pulse size not proportional to CNT.

By employing CNT, we need not require vacuum formation particularly for endoscopic type of therapy. In addition, we can adjust the average electron density to the laser as we wish to set, such as the near critical density to the selected laser wavelength, by choosing the specific diameter of CNT on the scale of a nanometer.

This flexibility of CNT parameter design can also facilitate research in the experimental stage, when we can take laboratory CPA (chirped pulse amplification – see section III) laser to show the effects of the CNT based near critical density LWFA and to study the laser parameters which can yield electron beam output of therapeutic quantity.

Beat-wave acceleration further enhances near-critical density LWFA

Two laser pulses with different frequencies can set up a scheme of beat-wave acceleration. This further enhances interaction between laser and plasma over many beats from the two laser frequencies. With this approach, it is found that laser intensity of 10^{14} W/cm^2 can accelerate electrons to energy of 10 keV order suitable for the proposed endoscopic accelerator. Extensive studies of this operation are given by E. Barraza-Valdez *et al* [7]. A set of suggested operating parameters is given as an example in figure 6.

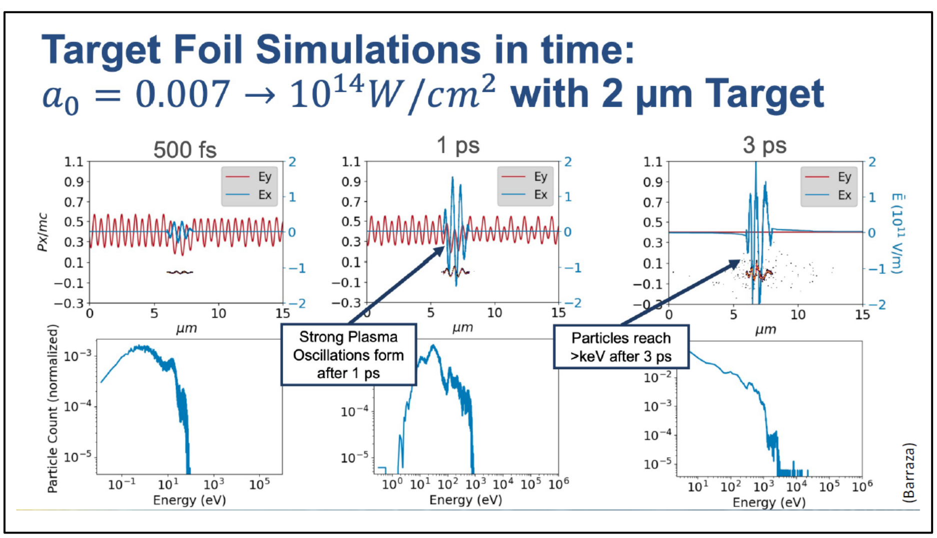

Figure 6. Laser parameter, wakefield magnitude, electron momentum and energy from beat-wave LWFA simulations for endoscopic accelerator. Studies are given in reference [7]. This plot is from private communication with E. Barraza.

Part III. Ultrafast fiber laser for the endoscopic electron accelerator

Plasma wakefield acceleration is driven by high-intensity laser pulses

Reviewed in Part II, acceleration of electrons comes from laser-driven wakefield in the plasma due to the intense laser pulse's pondermotive push that generates the strong space-charge field. These high-peak-power light pulses are produced by ultrafast lasers and amplifiers.

The high laser intensity brought to the accelerator medium is created from the two-fold energy focusing capabilities from the laser. One is the temporal "focusing" in the short pulses where light energy can be concentrated to the spikes of impulses. For example, a miniscule energy packet of 1 milli joule, when concentrated in one picosecond duration, carries peak power of one gigawatt. Second capability from the laser is spatial focusing capability from a coherent laser beam. "Focus like a laser", by using optical lenses, leads a laser beam to a micrometer-sized spot, or the focal point. Together, when a laser beam of gigawatt peak-power pulses is focused to a modest spot of 20 μm, for example, laser intensity will reach 3×10^{14} Watts/cm^2. At this intensity, the (oscillating) electric field in the laser pulse is greater than the binding electric field in a typical solid like SiO_2 or glass, and thus ionizes the solid. In the study of laser plasma wakefield acceleration presented in Part II, this intensity is sufficient to drive the endoscopic accelerator to the required electron energy on the order of 10 keV for therapy.

We reviewed in a recent publication [13] on the technology and industry of ultrafast fiber lasers relevant to laser wakefield medical applications. More details are given there about femtosecond lasers, fiber lasers, fiber delivery, enabling components, state and maturity of the technology. Here we aim to offer a snapshot of the technologies, compactization to fiber laser and real-world applications like femtosecond ophthalmology, applicable to the implementation of the proposed micron-scale medical accelerator.

Femtosecond lasers

An ultrafast laser system is illustrated in figure 7. This laser system was initially built in the University of Rochester Laboratory for Laser Energetics in 1980s. The photo was taken when the system was rebuilt in the Center for Ultrafast Science at the University of Michigan [14], showing the amplifier section. The red laser beam originates from the dye laser oscillator [15], which produces 100 fs (femtosecond, or 10^{-15} second) pulses. The green laser beam is the pump which transfers its energy to the red beam to be amplified. This laser system occupies two optical tables, delivers sub-gigawatt of peak power which, when focusing down, reaches an intensity of 10^{14} W/cm^2. It happens this is the laser intensity needed to drive the currently proposed endoscopic laser accelerator.

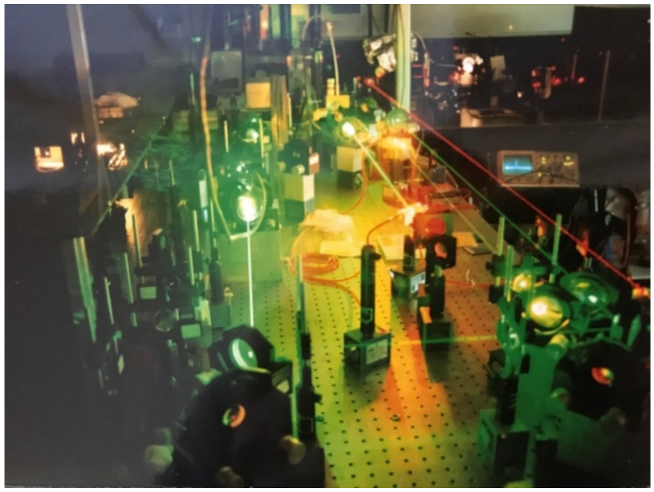

Figure 7. Femtosecond dye laser system which produced 100 fs, 200 mega-watt peak power. Focused beam had $10^{14}\ W/cm^2$ *peak intensity [14,154]*

The laser system in the figure is based on free-space optics. Today free-space platforms continue to construct higher peak-power lasers for scientific research. Most of the free-space ultrafast lasers are based on Ti:Sapphire, Nd:Glass or other solid-state laser gain materials and optics like mirrors, lenses, optical mounts, etc. Apparently, construction occupies larger volume due to bulk optics, mounts, vibration reduction mechanics etc.

Compactization – fiber lasers

A compact form of lasers has emerged in laser research and industry, based on guided optics of optical fiber and laser diodes. Fiber laser takes a thin strand of optical fiber, active or passive, and a diode laser as the pump source is built on a tiny yet powerful light-emitting semiconductor junction. Both forms of the lasers are constructed from wave-guiding principles. Bulk optics is eliminated from most parts in this type of laser construction and this compactness aids or necessitates portable field application. Fiber laser is the compact laser source for our proposed laser medical accelerator. We assess that it is the ready technology for the endoscopic therapy approach. An illustration of fiber laser is given in figure10.

Ultrafast fiber laser technology

Advances in ultrafast fiber lasers are reviewed by a number of excellent papers, for example, by Chang *et al* [16]. Fiber lasers have been advanced to become one of the major constructions of femtosecond lasers.

There are several key elements for ultrafast fiber lasers: 1) high-power laser diodes serve as reliable pump sources; 2) double-clad fiber increases laser brightness from broad-area diode emitters to fiber; 3) large-mode-area gain fiber [17] reduces intensity in amplifiers ; 4) chirped pulse amplification [2] is a must to manage nonlinearity (in fact nonlinearity appears at lower peak power levels in fiber lasers than free-space lasers due to fiber's small core area and very long interaction). For all of the above, single spatial mode (except for the pumps) must be upheld throughout to maintain spectral and spatial coherence for diffraction-limited temporal and spatial focus.

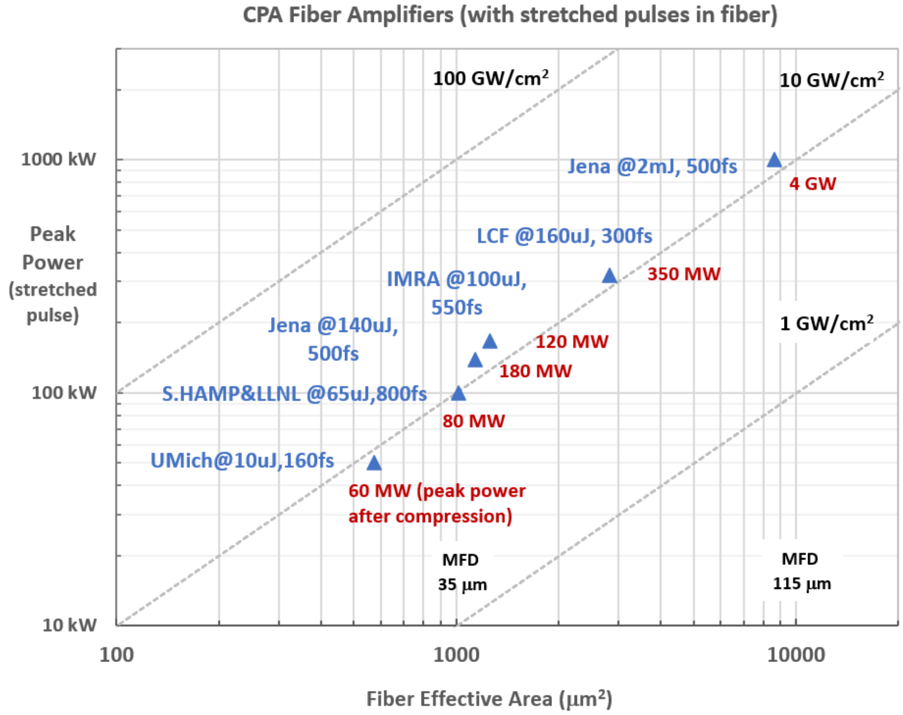

Figure 9. Survey of research work in CPA ultrafast fiber amplifiers from a number of publications in this limited survey. Triangle data points mark reduced peak power of stretched pulse in fiber amplifiers. Blue notations are the resulted output pulse energy and pulse width after compression and the corresponding output peak power is marked in red. Output peak power up to 4 GW is seen increasing with fiber effective area. The ratio of instantaneous power (stretched) in vertical axis over fiber area in horizontal axis is light intensity in fiber. Blue triangle data points are seen following along the intensity line of 10 GW/cm^2, indicative of the limit imposed by nonlinear phase accumulation [13].

Ultrafast fiber amplifier is constrained, due to the nonlinearity in glass material of fiber, to intensity of about 10^{10} W/cm^2. In figure 9, a survey of research works is illustrated [13]. Peak power management from CPA and large-core fibers have pushed up peak power output from fiber lasers beyond GW. Practical systems can produce tens and hundreds of megawatts or even gigawatt level, which can deliver the intended intensity of 10^{14} W/cm^2 at focus for our endoscopic laser-electron accelerator.

Coherent combination of fiber fibers[18] is a forefront of fiber laser research where 61 fiber laser coherent combinations have been demonstrated [19] as shown in figure 10. Each individual fiber amplifier is kept within the nonlinearity limit of the material and the coherently combined output delivers higher peak power and average power much beyond what a single fiber amplifier can reach.

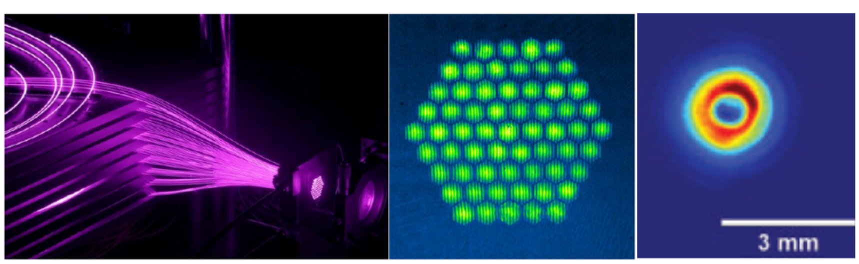

Figure 10. XCAN 61 channel CBC laser. The bundle of 61 YB doped 30 µm MFD amplifying fiber can be seen fluorescing. The fibers are arranged in the laser head in a honey-comb distribution and subsequently collectively collimated through a lenslet array (far right of the left image). Collective phase delays recording through interference pattern (right). Adapted from [ref. 19].

Fiber laser applications in the real world

In table 1, we list a number of applications (proposed endoscopic LWFA is added in). Listing *peak* laser intensity from low to high, metal cutting uses thermal power offered by the continuous-wave (CW) fiber lasers with average-power up to 100 kW. The high wall-plug efficiency of 50% showcases the practical capabilities of fiber lasers pumped by laser diodes. Q-switched fiber lasers (nanosecond pulse width) for semiconductor processing produce nanosecond pulses, pushing up laser peak intensity to 10^9 W/cm^2. Further increasing to 10^{13} W/cm^2 level by ultrafast (picosecond or femtosecond pulse width) lasers and amplifiers, laser interacts with material by way of cold ablation [20] which ionizes (vaporizes in effect) solid without collateral thermal damage. Glass cutting of smart phone screens are in mass production using laser-precision micromachining for super-fine edges. Now many manufacturing laser-cutting systems are fiber-laser based.

Application	Average Power	Pulse Width	Peak Power	Spatial Mode	Focused Intensity
Metal cutting (heat)	1 to 100 kW	Continuous	same as average	MM[1]	10^7 W/cm^2 (CW)
Semiconductor Processing	10 to 1000 W	1 to 100 ns	MW (10^6 W)	MM/SM[2]	10^9 W/cm^2 (peak)
Glass cutting (cold ablation)	> 10 W	≤ 0.5 ps	Hundreds of MW	SM	10^{13} W/cm^2 (peak)
Femtosecond Ophthalmology	10 to 30 mW	≤ 1 ps	10 MW	SM	10^{13} to 10^{14} W/cm^2 (peak)
Endoscopic LWFA (>10 keV electrons)	~1 W	≤ 1 ps	≥ GW (10^9 W)	SM	≥ 10^{14} W/cm^2 (peak)

[1]MM: multi-mode (spatial) [2]SM: single mode

Table 1 Fiber laser applications

Femtosecond ophthalmology

Continuing on the list in table 1, LASIK (laser-assisted in situ keratomileusis) provides one of the best examples of ultrafast lasers in medical applications [21]. Based on the same mechanism of laser ablation (material under laser exposure is ionized and removed without experiencing the thermal damage from the laser), the surgeon uses ultra-short pulses from the laser create a flap in the cornea during LASIK eye surgery. The femtosecond laser replaces the microkeratome used in traditional vision correction surgery, known as bladeless LASIK. Note the low average power (10 to 30 mW) used in LASIK procedure. Since the FDA approved LASIK in 1991, 20–25 million eyes have been treated.

The laser for LASIK is a mode-locked, diode-pumped Nd:glass oscillator and amplifier system which output is laser pulses of 600 fs up to 7 μJ [22] . LASIK operates at laser intensity of a few times of 10^{13} W/cm^2. FDA approved LASIK system took place prior to commercial ultrafast fiber lasers which can now deliver same performance.

Commercial turn-key fiber laser systems and available subsystems and components

Volume applications in glass cutting has pushed the commercial productization of fiber lasers with great improvements in reliability and realistic costs. There are commercial turn-key systems in the marketplace [23]. At the same time, many subsystems and components are available when we consider making custom laser for the proposed endoscopic accelerator at the implementation stage. Intended laser intensity at 10^{14} W/cm^2 is within the reach of ultrafast fiber technology.

Part IV. Delivering intense laser pulses to the tip of endoscope

As discussed in Part III, fiber lasers and amplifiers are capable of producing the needed gigawatt peak power and subsequently the peak intensity for the LWFA medical accelerator. In the endoscopic application, laser pulses are to be delivered with flexible light channel to the laser accelerator at the tip of endoscope near the treatment site. However, these laser pulses of the peak power for our proposed use cannot be carried by conventional optical fiber. Alternatively, we look to recent innovations in hollow-core fibers to flexibly deliver the light bursts.

Laser peak power exceeds conventional solid-core fiber limits

Conventional optical fibers utilize total internal reflection to guide light waves, with higher index core surrounded by lower index cladding. These are the solid-core fibers with the core exposing to the peak intensity of laser's transverse gaussian profile. For example, when considering propagation of a moderate 200 MW peak power of light pulses for our proposed endoscopic accelerator, the core (for example in 20 μm mode-field diameter(MFD)) experiences an intensity of 5×10^{13} W/cm^2 which is 3 orders of magnitude higher than the nonlinearity limit of 10^{13} W/cm^2 in glass [20]. Not only that, it is also near or above glass breakdown threshold 10^{13} W/cm^2 where instantaneous electric filed is greater than the bonding field.

Innovative hollow-core fiber (HCF)

Hollow-core fiber innovation stems from the advents of photonic crystal fiber (PCF) technology. PCF pushes fiber construction beyond conventional design with simple index profile in the radial direction, by introducing a microscopic crystal (periodic) structure of optical index in the fiber. Photonic crystal fiber design branches to two distinct mechanisms: *high-index* guiding and *low-index* guiding. Large-mode-area fibers [17] enabling ultrafast fiber lasers and amplifiers are based on *high-index* guiding based on total internal reflection. Hollow-core fiber designs belong to *low-index* guiding, or photonic bandgap guiding.

Photonic bandgap light guiding is fundamentally different from effects based on total internal reflection. The light is typically confined to the empty core such as air while the surrounding microstructure region as the cladding displays a photonic bandgap [24,25]. Like electron waves in a solid crystal where a band of electron wavevectors is forbidden, optical waves of certain wavelengths in the photonic bandgap crystal are anti-resonant. In HCF, central airy core is surrounded by the anti-resonant (thus being reflective) microstructure cladding. Light of specific wavelengths can only propagate in the hollow core. Only the tail of the transverse profile (less than a few percent of the light intensity) interacts with the glass material [26a].

Hollow-core fiber delivery for intense ultrafast laser pulses

We are encouraged to see commercial HCFs are emerging and some products are designed specifically to transmit intense ultrafast laser pulses. In products offered by PT Photonics Tool [26a, 26b], such HCF patch cable delivers laser pulse peak power up to our desired target around one gigawatt for meters of length with fractional loss. Bending radius is 25 cm, practical for industrial or endoscopic applications. An example is shown in Figure 11 (See attached).

Figure 11. A hollow-core fiber example by PT Photonics Tools [ref.26b]. One end is the launch and the other end is the delivery point where microscopic accelerator can be placed, perspectively, inside a patient's body. Bending radius is about 25 cm, quite realistic for the application. (Photo with PT Photonics Tools permission)

In their performance characterization and specification [27], it was shown that 500 μJ of pulse energy can be carried throughout the gigawatt peak power level which facilitates focused intensity above 10^{14} W/cm^2. Average power is up to 20 Watts which is also adequate for producing sufficient dose rate for our proposed endoscopic treatment.

Add discussions to recent development of research work[26c] from Heriot-Watt University and University of Southhampton, which pushes up capability of hollow-core/anti-resonant fiber to deliver laser intensity at 10^{15} W/cm^2 and higher.

Laser intensity and beam focus

With capabilities to flexibly bring laser pulses to the tip of endoscope, the final task is to have the best options to focus on the accelerator's target at desired laser intensity. A number of factors influence the focus setup. We know that fast optics is required to provide tight focal spot for best light intensity to drive the plasma accelerator, and at the same time to consider suitable beam size at the lens to avoid damage of lens material.

Focusing optics is a crucial development and also, we need to consider designs from a system viewpoint, including the parameters of laser source, hollow-core fiber limits, dispersion management, LWFA target parameters etc. Here, let us discuss the requirements with different focal spot diameters at 5 μm, 10 μm and 20 μm to achieve the same intensity of 3×10^{14} W/cm^2. The tighter focal spot (5 μm), the more demanding for the focusing optics on aberration control, tolerance and lens construction, but requires less peak power from the laser source and delivery (50 MW peak power). In contrary, larger focal spot (20 μm) exerts less requirements on the focusing optics but pushes up laser peak power (1 GW) demanding more on the laser and delivery fiber. Therefore there will be trade studies in engineering the implementations of the endoscopic accelerator.

In the recent decade, there are much active research in a new branch of optics involving optical metasurfaces. Metasurfaces with subwavelength thickness hold considerable promise for novel optical applications due to their unprecedented ability to control the phase, amplitude, and polarization of transmitted, reflected, and diffracted light [28]. There are potentials from these innovations that can be applied to micro-optics related to beam focusing, dispersion management, beam shaping etc. for the micron-scale laser electron accelerator in this proposal.

Summary Part I through Part IV – Putting it together

We review the current understanding theoretically on near critical density laser wakefield acceleration with carbon nanotubes (CNT) as the solid plasma target. Based on this principle of operation, laser accelerator of micron-scale can deliver 10 keV to 100 keV electron energy, which can penetrate microbic thickness of cancer cells when irradiating directly to destroy the tumor. We can then install the accelerator at the tip of an endoscope.

To realize the endoscopic accelerator, we survey the femtosecond lasers technologies. The compactness and readiness of ultrafast fiber lasers and hollow-core fibers are reviewed. An implementation scheme is illustrated in figure 12, where the fiber laser produces light pulses, the hollow-core fiber flexibly delivers the pulses to the tip of endoscope inside a patient's body and the laser pulses drives the accelerator of nano-material target releasing energic electrons to eradicate tumor cells.

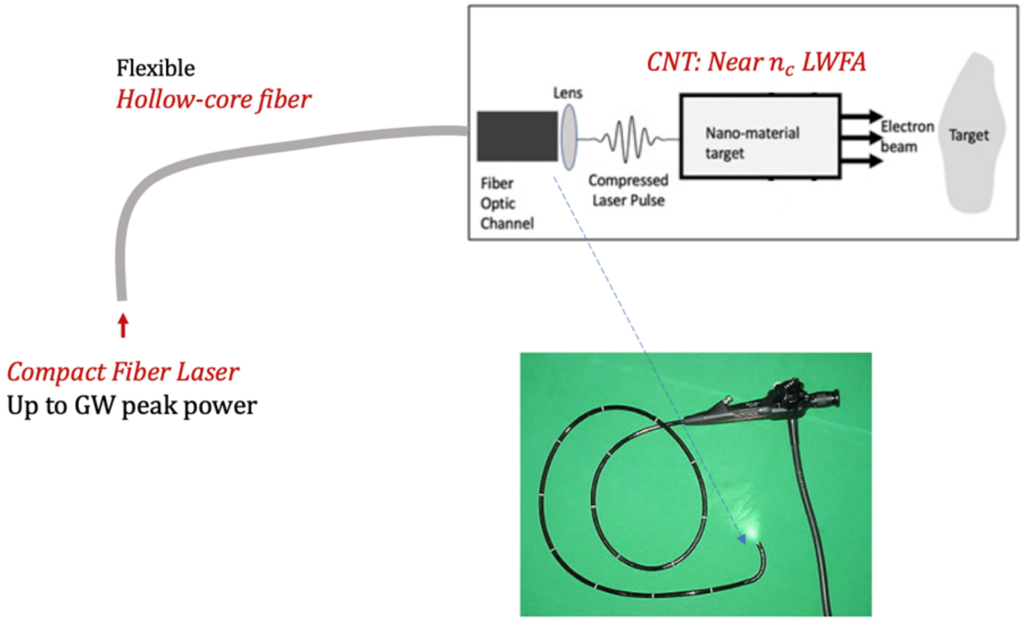

Figure 12. Implementation concept of the proposed endoscopic laser accelerator. A generic endoscope picture is used to aid the visualization of the concept apparatus.

Many of the cited works in this white paper are also included in "Progress of Laser Accelerator and Future Prospects" in a special issue of Photonics [29].

Part V. Possible applications to other diseases

Other diseases other than radiotherapy of cancer such as cardiology (angioplasty), stroke, arthritis, macular degeneration by the present approach that has been developed above are now considered to be potential applications of the present method. Now that we have developed a tiny accelerated electron source for radiotherapy of cancer is driven by a fiber laser that could be insertable into a patient organ where tumor tissues may be developing, we are expanding our vision beyond this cure of cancer. Such a device may be insertable to a portion of an artery and / or heart as well. If so, we address a different class of diseases that may be handled by the *in-situ* electron source in such an organ. Such an electron source *in-situ* shines upon a clot in the artery that could melt such a structure away. This entails the application of such a microscopic electron source to the cure of angioplasty and the clot dissolution to tackle a possible strike, for example.

++++++++++++++++++++(we were writing a very preliminary communication below on this subject. Yesterday 11/19/24, I received a fuller note from Jeffrey on this subject. Thus I attach his note below (*))+++++++++++++++++++

(Jeffrey: I need you description beyond this. I suppose that the description can be, at this stage of this paper, still speculative, though visionary. I certainly need references to each disease and the current cure, which this method could supplement or overtake. At least one for each disease and one for the current orthodox cure. With these in, we can at least present a possibility.)

Potential applications of the miniature LWFA source (not in an organized way) as discussed in Nov. 11 meeting (a rough note)

We recognize that there are 800,000 heart disease patients, 8% for treatment. This indicates that if we consider to employ the present micron-scale electron therapy at the tip of an endoscopy to some of such patients, it may have an interest to consider such in deeper investigations for the future. See for example refs.[30], [31]. [32].

Endoluminal intracoronary therapy (heart disease)

References:

Endoluminal beta-radiation **therapy** for the prevention of coronary restenosis after balloon angioplasty. The Dose-Finding Study Group.

Verin V, Popowski Y, de Bruyne B, Baumgart D, Sauerwein W, Lins M, Kovacs G, Thomas M, Calman F, Disco C, Serruys PW, Wijns W; Dose-Finding Study Group.N Engl J Med. 2001 Jan 25;344(4):243-9. doi: 10.1056/NEJM200101253440401.PMID: 11172150 **Free article.** Clinical Trial. [30]

[**Endoluminal** beta-radiation **therapy** for the prevention of coronary restenosis after balloon angioplasty. Localized **intracoronary** gamma-radiation **therapy** to inhibit the recurrence of restenosis after stenting].

Bernardi G.Ital Heart J Suppl. 2001 May;2(5):559-62. [31]

High-dose **intracoronary** irradiation after de novo stent implantation results of the EVEREST (Evaluation of **Endoluminal** Radiation in Elective Stenting) trial.

Geiger MH, Ludwig J, Burckhard R, Scheinert D, Müller RG, Daniel WG, Sauer R, Strnad V.Strahlenther Onkol. 2006 Jan;182(1):9-15. doi: 10.1007/s00066-006-1434-y.PMID: 16404515 Clinical Trial. [32]

In addition, we can contemplate the employment of our present approach to be applied to the treatment of arrhythmia, a heart disease. Thwi would take a treatment on the order of 25-25 Gy irradiation. See for example, refs. [33], [34], and [35]

Application to Cardiac Arrhythmia Treatment

The application of radiation therapy to cardiac arrhythmias—particularly ventricular tachycardia (VT)—represents one of the most promising extensions of the technology beyond cancer treatment. Recent clinical studies have shown remarkable efficacy, challenging traditional treatment paradigms and offering new possibilities for patients with treatment-resistant arrhythmias.

Remarkable Efficacy in Initial Studies

Initial research has demonstrated unprecedented effectiveness of radiation therapy for cardiac arrhythmias. A single-fraction 25Gy treatment (Phillip et al. 2017) produced a dramatic 99.9% reduction in Ventricular Tachycardia (VT) episodes. This success rate far exceeds conventional treatment approaches for recurrent VT.

Confirmed in Larger Clinical Trials

These promising initial results have been validated in more extensive studies. The ENCORE-VT Phase I/II trial, which included 19 patients, demonstrated approximately 94% decrease in arrhythmia episodes in a controlled clinical setting. The trial confirmed that radiation therapy could effectively treat arrhythmias that were resistant to conventional interventional approaches.

Ongoing Research Initiatives
Current research is expanding our understanding through several important initiatives:

1. **STOPSTORM Project**: This multi-center collaborative research across Europe focuses on expanding patient data and evaluating long-term outcomes. Key concerns being investigated include potential late complications such as coronary artery damage and impacts on cardiac function.

2. **RADIATE-VT Trial**: Currently in progress, this Phase 2 pivotal trial ("Cardiac RADIoablation Versus Repeat Catheter Ablation") sponsored by Varian Medical Systems represents a significant step toward potential widespread clinical adoption.

Mechanisms of Action
The traditional understanding of radiation therapy for cardiac arrhythmias suggested that high-dose radiation disrupts abnormal electrical conduction pathways primarily through fibrosis (scar formation). However, clinical observations challenge this understanding:

1. Clinical doses (~25 Gy) cannot create scars equivalent to catheter ablation, yet VT patients show dramatic reduction in arrhythmias within days to weeks.

2. This timeline is too rapid to be explained by completed fibrosis, which typically takes months to years to fully develop.

Research now indicates a two-phase process:

1. **Acute Phase (Days to Weeks)**: Characterized by electrophysiological remodeling:
   - Increased expression of sodium channels (Na_v1.5) by approximately 80%
   - Increased expression of connexin43 (Cx43)
   - Enhanced myocardial conduction velocity

2. **Chronic Phase (Months to Years)**: Fibrosis develops, serving as an insulator to permanently block the abnormal circuit.

The key relationship governing this process is: Excitation wavelength = Conduction velocity × Refractory period. By enhancing conduction velocity in the acute phase, radiation therapy effectively disrupts the reentry circuits that cause arrhythmias.

Challenges to Widespread Adoption
Despite promising clinical results, several barriers currently limit widespread adoption:

1. **Departmental Barriers**: Separation between cardiology and radiation oncology departments creates institutional challenges.

2. **Capacity Limitations**: Radiation oncology departments typically handle 50-100 patients per day, making it difficult to integrate new treatment categories.

3. **Cost Factors**: The high cost of linear accelerators and protected rooms (approximately $6M = $5M for the machine + $1M for the protected room) presents significant financial barriers.

Potential of Laser-Plasma Technology

The laser-plasma technology described in this paper could address these limitations by enabling radiation to be emitted from the tip of a catheter. This approach offers several advantages:

1. **Direct Access to Deep-Seated Lesions**: Compared to external radiation, catheter-based delivery makes it easier to concentrate the dose precisely on the target while reducing exposure to surrounding normal tissues.

2. **Elimination of Departmental Barriers**: By integrating the technology into catheter-based procedures already performed by cardiologists, interdepartmental coordination is minimized.

3. **Leveraging Existing Expertise**: The approach can utilize expertise from existing catheter ablation procedures, such as identification of arrhythmia circuits through electrical mapping, followed by precise radiation delivery.

The integration of our proposed laser-plasma technology with cardiac catheterization represents a promising frontier in the treatment of ventricular tachycardia and potentially other cardiac arrhythmias, offering a non-destructive alternative to traditional ablation methods.

Arrhythmia (heart disease). Treatment 25 – 35 Gy

References:

Cardiac Arrhythmias: Diagnosis, Symptoms, and Treatments.

Fu DG.Cell Biochem Biophys. 2015 Nov;73(2):291-296. doi: 10.1007/s12013-015-0626-4.PMID: 25737133 [33]

Editorial commentary: Stereotactic ablative **radiotherapy** for **cardiac arrhythmia** - A rising STAR?

Krug D, Blanck O, Dunst J, Bonnemeier H.Trends Cardiovasc Med. 2022 Jul;32(5):297-298. doi: 10.1016/j.tcm.2021.05.002. Epub 2021 May 29.PMID: 34062260 No abstract available. [34]

Stereotactic **arrhythmia** radioablation: A novel therapy for **cardiac arrhythmia**.

Wang S, Luo H, Mao T, Xiang C, Hu H, Zhao J, Wang X, Wang J, Liu H, Yu L, Jiang H.Heart Rhythm. 2023 Sep;20(9):1327-1336. doi: 10.1016/j.hrthm.2023.04.052. Epub 2023 May 5.PMID: 37150313 Review. [35]

We are expanding our view from the heart issues to arteries. Then let us take a look at the vascular artery treatment, such as the electron coronary artery treatment by the present approach. See such ref. [36]. It may be also useful to take a look at the arteriovenous malformation (an artery diseases) by such an approach. See refs. [37], [38], and [39].

Vascular artery, electron coronary artery (artery disease)

References:

Coronary arteries.

Wielopolski PA, van Geuns RJ, de Feyter PJ, Oudkerk M.Eur Radiol. 1998;8(6):873-85. doi: 10.1007/s003300050484.PMID: 9683689 Review. [36]

Arteriovenous malformation (artery disease)

References:

Treatment of Brain **Arteriovenous Malformations.**

Beneš V, Bubeníková A, Skalický P, Bradáč O.Adv Tech Stand Neurosurg. 2024;49:139-179. doi: 10.1007/978-3-031-42398-7_8.PMID: 38700684 [37]

De Novo Development of Moyamoya **Disease** after Stereotactic Radiosurgery for Brain **Arteriovenous Malformation** in a Patient With RNF213 p.Arg4810Lys (rs112735431).

Torazawa S, Miyawaki S, Shinya Y, Kawashima M, Hasegawa H, Dofuku S, Uchikawa H, Kin T, Shin M, Nakatomi H, Saito N.World Neurosurg. 2020 Aug;140:276-282. doi: 10.1016/j.wneu.2020.05.068. Epub 2020 May 17.PMID: 32434013 [38]

Predictive Factors for **Arteriovenous Malformation** Obliteration After Stereotactic Radiosurgery: A Single-Center Study.

Erickson N, Mooney J, Salehani A, Thomas E, Ilyas A, Rahm S, Maleknia P, Yousuf O, Fiveash J, Dobelbower C, Fisher WS 3rd.World Neurosurg. 2022 Apr;160:e529-e536. doi: 10.1016/j.wneu.2022.01.060. Epub 2022 Jan 22.PMID: 35077887 [39]

We now take a look into eye diseases below. One example may be our approach applicability toward the macular degeneration (eye disease). See reefs. [40], [41], and [42].

Macular degeneration (eye disease)

References:

LIGHTSITE III: 13-Month Efficacy and Safety Evaluation of Multiwavelength Photobiomodulation in Nonexudative (Dry) Age-Related **Macular Degeneration** Using the Lumithera Valeda Light Delivery System.

Boyer D, Hu A, Warrow D, Xavier S, Gonzalez V, Lad E, Rosen RB, Do D, Schneiderman T, Ho A, Munk MR, Jaffe G, Tedford SE, Croissant CL, Walker M, Rückert R, Tedford CE.Retina. 2024 Mar 1;44(3):487-497. doi: 10.1097/IAE.0000000000003980.PMID: 37972955 **Free PMC article.** Clinical Trial. [40]

Stereotactic **radiotherapy** for wet age-related **macular degeneration**: current perspectives.

Neffendorf JE, Jackson TL.Clin Ophthalmol. 2015 Sep 28;9:1829-34. doi: 10.2147/OPTH.S75638. eCollection 2015.PMID: 26491243 **Free PMC article.** Review. [41]

Radiotherapy for neovascular age-related **macular degeneration.**

Evans JR, Igwe C, Jackson TL, Chong V.Cochrane Database Syst Rev. 2020 Aug 26;8(8):CD004004. doi: 10.1002/14651858.CD004004.pub4.PMID: 32844399 **Free PMC article.** [42]

We extend our consideration of the present technological developments toward the liver metastases (liver disease) . See the refs. [43], [44], and [45]. It should apply to the hepatocellular cancer. See Refs. [46]. [47], and [48].

Liver metastases (liver disease)

References:

[Stereotactic body **radiotherapy** for **liver metastases**.]

Aitken KL, Hawkins MA.Clin Oncol (R Coll Radiol). 2015 May;27(5):307-15. doi: 10.1016/j.clon.2015.01.032. Epub 2015 Feb 12.PMID: 25682933 Review. [43]

External-beam **radiotherapy** in the management of **liver metastases**.

Malik U, Mohiuddin M.Semin Oncol. 2002 Apr;29(2):196-201. doi: 10.1053/sonc.2002.31675.PMID: 11951218 Review. [44]

The Management of Colorectal Cancer **Liver Metastases**: The Radiation Oncology Viewpoint.

Barry A, Wong R, Dawson LA.Int J Radiat Oncol Biol Phys. 2019 Mar 1;103(3):540-541. doi: 10.1016/j.ijrobp.2018.10.010.PMID: 30722966 No abstract available. [45]

Hepatocellular cancer (liver disease)

References:

Evolution of Response-Based **Radiotherapy** for **Hepatocellular Cancer**.

Elaimy AL, Cao Y, Lawrence TS.Cancer J. 2023 Sep-Oct 01;29(5):266-271. doi: 10.1097/PPO.0000000000000679.PMID: 37796644 **Free PMC article.** Review. [46]

The role of external beam **radiotherapy** in the treatment of **hepatocellular cancer**.

Chino F, Stephens SJ, Choi SS, Marin D, Kim CY, Morse MA, Godfrey DJ, Czito BG, Willett CG, Palta M.Cancer. 2018 Sep 1;124(17):3476-3489. doi: 10.1002/cncr.31334. Epub 2018 Apr 12.PMID: 29645076 **Free article.** Review. [47]

Stereotactic Body **Radiotherapy** for **Hepatocellular** Carcinoma.

McPartlin AJ, Dawson LA.Cancer J. 2016 Jul-Aug;22(4):296-301. doi: 10.1097/PPO.0000000000000201.PMID: 27441750 Review. [48]

(*) ++++++++++(below is the note I received from Jeffry as of 11/19/24; A simple version of these suggestions has been inserted above in Part V. 12/18/24)++++++++++

Based on such an opportunity, the followings are a list of such possibilities of miniature sized high density LWFA driven via fiber laser. We list 7 such proposed suggestions.

Proposed application #1: replace current radionuclide based brachytherapy with electronic brachytherapy

1. Extensively discussed in the earlier paper [5].

Proposed application #2: re visit intracoronary brachytherapy for coronary restenosis

1. Intracoronary brachytherapy for instent restenosis was already developed about 1998-2001 but was inferior to drug eluting stents and was significantly more resource burdensome since it required two disciplines. Only significantly superior results would have justified its continuation
2. The drug eluting stents work well but still have about an 8% failure rate and so a very few centers still perform intracoronary brachytherapy for instent failures after drug eluting stents.
3. This would be 8% of the approximately 60,000 procedures or about 4800 procedures a year which is not a lot in the cardiology world so a brachytherapy system would need to be relatively inexpensive and simple to use to encourage its adoption

Proposed application #3: apply endovascular brachytherapy for other kinds of restenosis

1. Renal arter
2. AV fistulas for diabetes

Proposed application #4: “non destructive cardiac ablation” for cardia arrythmias

1. Currently about 70,000 cardiac ablative procedures per year in the United States
2. Current technology uses destructive methods (RF, cryotherapy, or pulsed field ablation)
3. External beam radiosurgery used for cardiac ablations who are not candidates for destructive procedures
4. Intracardiac non destructive radiosurgery may be better than destructive procedures (fewer complications)

Proposed application #5: “non destructive” radiosurgery for cerebral arteriovenous malformations

1. There aren’t a large number of cerebral AVMs so AVMs don’t meet the high incidence criteria for a potential application but there is a sizable literature for radiosurgery treatments
2. Catheter microembolization is a common therapy but has limitations and complications
3. The application of miniature radiation sources into the AVM niduses may be a way to treat even large AVMs (limited by external beam dose to the surrounding brain tissue) without the ischemic limitations of embolic therapies
4. Even if the currently proposed Laser Wakefield technology can’t support the application of volume or line sources in very small vessels the technology may be developed at some point

Proposed application #6: other “non destructive” ablations

1. Catheter based electronic brachytherapy may be a way to ablate lesions (liver, lungs, kidneys) without thermal or electrical tissue destruction and also without external beam radiation therapy
2. Approximately 20,000 new diagnoses of HCC per year and only a minority undergo some form of liver ablation (i.e. microwave, Radiofrequency, chemical, electroporation)
3. More metastases ablated
4. Destructive technologies are limited by vascular proximity
5. Established literature for external beam radiosurgery to draw from and a few studies of intraoperative brachytherapy

Proposed application #7: macular degeneration

1. Most common cause of age related vision loss (age related macular degeneration)
2. Approximately 18 million in the U.S.

3. Most patients at least 70% receive antiangiogenic drugs (anti-VEGF meds)
4. About 5% undergo laser or photodynamic therapy about 5-6000 per year
5. External beam radiation therapy promising in clinical trials but not tested more widely.
6. IRay system for macular degeneration was/is an office based wall power radiation system that nobody has ever heard about and might be an example of mistakes to avoid in implementing a Laser Wakefield system

(from HamamatsuU.)

a) Arrhythmia Section

I suggest adding a comprehensive review of landmark studies, particularly:

The breakthrough study by Cuculich et al. demonstrated radiation therapy's effectiveness for VT resistant to catheter treatment, showing 0.1% recurrence rate at 12 months with 5 patients [48-1]. This is particularly significant when compared to conventional methods showing approximately 50% recurrence rate at 6 months [48-2,48-3]. The subsequent ENCORE-VT trial [48-4] further validated these findings, with 17 of 18 patients (94%) who survived to 6 months achieving reduction in VT episodes or PVC burden. Currently, the more extensive RADIATE-VT trial is in progress [48-5].

b) Renal Denervation

Current catheter-based ablation approaches, such as radiofrequency ablation, have evolved from early trials showing limited success [48-6] to more recent studies demonstrating significant efficacy using improved multi-electrode systems [48-7], achieving blood pressure reductions of -4.0 mmHg compared to sham procedures. Ultrasound ablation [48-8] has shown promising results with slightly greater blood pressure reductions of -6.3 mmHg, offering non-contact energy delivery. The breakthrough study using Stereotactic Body Radiotherapy (SBRT) has demonstrated that radiation can potentially achieve even greater efficacy in renal denervation [48-9], showing blood pressure reductions of -12.0 mmHg in preclinical studies. While these results are from animal studies and require clinical validation, they suggest radiation therapy's significant potential in this field. However, external beam radiation has limitations in terms of precise targeting and potential effects on surrounding tissues. Miniature LWFA could potentially enhance this therapeutic approach by enabling catheter-based radiation delivery, combining the promising effectiveness of radiation therapy with minimally invasive techniques. The advantages include:

- Precise radiation delivery without requiring direct tissue contact
- Controlled treatment depth through electron energy modulation
- Real-time adjustment of treatment delivery
- Minimal impact on surrounding tissues

It is encouraging to see such a view point of new applications and areas of diseases other than electron radiotherapy of cancer. We need further discussions on these.

Part VI. Conclusions

The introduction of LWFA [1] and the chirped pulse amplification [2] have greatly comverted the conventional accelerators into far more compact laser accelerators. Thus it is plausible to use laser accelerators toward some class of electron radiotherapy of cancer, such as the Very High Energy Electron (VHEE) therapy driven by LWFA [49]. It has been also noticed before that LWFA-driven radiations, such as X-rays and betatron radiations (lower energy photons than gamma-rays / X-rays) have been considered and used for medical applications. For example, There are series of works of gamma (or X-rays) emissions from LWFA electrons for intraoperative radiation therapy (IORT) by Gulietti (2008) [50], Grittani et al., (2016)[51], and Albert (2016) [52]. Meanwhile, the lower frequency EM radiation arising from LWFA accelerated electrons emitting betartron raditions. These have been considered for therapy or diagnosis: Such as Hussein et al. (2009) [53] and Kieffer et al. (2023) [54].

We now notice that if the LWFA can be further compactified, it could be insertable inside of the patient, rather than the electron irradiation outside of the patient. Toward this vision in this paper we further advance and improve both the operation of the LWFA by introducing the high density (near-critical density) regime interaction [7,8] which reduces the acceleration length and the compactification of laser from table-top CPA toward the fiber laser technology [13] [18]. We have introduced concrete steps and realizations of these processes [20][21][22][23]24][25][26]to realize a very compact fiber-laser driven electron accelerator that may be insertable into a patient at the tip of an endoscope. This new approach should usher in a new mode of electron radiotherapy of cancer with the inserted endoscope so that the operation of surgery is upon the *ins-situ* observation of the actual tumors and is also to avoid the irradiation of healthy tissues upon the paths of electrons in the conventional radiotherapy from outside of the patient body. Thus, this mode of operation should bring in a new wide array of applications of laser therapy (just as the LASIK [21] has done on ophthalmology therapy).

Encouraged by the above progress, we have added suggestions for a future development of such tiny and insertable accelerated electron sources toward the cure of other diseases beyond cancer. These include: possible cure of angioplasty (heart attacks), artery clots, symptoms of arthritis, and some classes of eye diseases. It is important that we should start such possibilities to see what kinds of tasks and how we can address these in the future.

Acknowledgement

The two of us (TT and WS) have originally participated and presented the works described in section I through section IV in the Symposium LUMIÈRE ET LASER (LIGHT AND LASER) À SAINT-MARTIN DE PALLIÈRES in Aug., 2024, which was organized by one of us (GM). The nature of this White Paper is exploratory, cross-disciplinary, and projecting our views into the future. Because of this, it is an open publication by the many volunteers to this endeavor so far. A part of the work was supported by the Rostoker Fund at UCI. We also thank Dr. A. Rudolf for his generous discussions on HCF.

References

[1] Tajima, T. & Dawson, J. M. Laser electron accelerator, Phys. Rev. Lett. 43, 267–270 (1979).

[2] Strickland, D. & Mourou, G. A. Compression of amplified chirped optical pulses, Opt. Comm. 55, 447–449 (1985).

[3] T. Tajima, K. Nakajima, and G. Mourou, Laser Acceleration, Rivista del Nuovo Cimento 40, 33 (2017) and references therein.

[4] K. Matsumoto, H. Saitoh, T. Doan A. Shiro, K. Nakai, A. Komatsu, M. Tsujimoto, R. Yasuda, T. Kawachi, T. Tajima, F. Tamanoi, Destruction of tumor mass by gadolinium-loaded nanoparticles irradiated with monochromatic X-rays: Implications for the Auger therapy, NatureResearch Scientific Report, 2019, https://doi.org/10.1038/s41598-019-49978-1

[5] Roa, D.; Kuo, J.; Moyses, H.; Taborek, P.; Tajima, T.; Mourou, G.; Tamanoi, F. Fiber-Optic Based Laser Wakefield Accelerated Electron Beams and Potential Applications in Radiotherapy Cancer Treatments. Photonics 2022, 9, 403.

[6] T. Tajima, Laser Wakefield Accelerators and their Applications to Medicine, presented at the Symposium LUMIÈRE ET LASER À SAINT-MARTIN DE PALLIÈRES

[7] E. Barraza-Valdez, T. Tajima, D. Strickland, and D. Roa, Laser Beat Wave Acceleration near Critical Density, Photonics 9, 476 (2022). doi:10.3390/photonics9070476

[8] B. Nicks, E. Barraza-Valdez, S. Hakimi, K. Chesnut, G. DeGrandchamp, K. Gage, D. Housley, G. Huxtable, G. Lawler, D. Lin, P. Manwani, E. Nelson, G. Player, M. Seggebruch, J. Sweeney, J. Tanner, K. Thompson and T. Tajima, High-Density Dynamics of Laser Wakefield Acceleration from Gas Plasmas to Nanotubes. Photonics 2021, 8, 216. https://doi.org/10.3390/photonics8060216

[9] M. Mori, E. Barraza-Valdez, H. Kotaki, Y. Hayashi, M. Kando, K. Kondo, T. Kawachi, D. Strickland, T. Tajima, Experimental realization of near-critical-density laser wakefield acceleration: Efficient pointing 100-keV-classelectron beam generation by microcapillary targets. https://doi.org/10.1063/5.0180773

[11] Iijima, S. Helical Microtubules of Graphitic Carbon. Nature 1991, 354, 56–58. https://doi.org/10.1038/354056a0

[12] Chattopadhyay, S., Mourou, G., Shiltsev, V.D., Tajima, T. (Eds.) Beam Acceleration in Crystals and Nanostructures (World Scientific: Singapore, 2020); ISBN 9789811217135.

[13] W. Sha, J.-C. Chanteloup, G. Mourou, Ultrafast Fiber Technologies for Compact Laser Wake Field in Medical Application. Photonics 2022, 9, 423. https://doi.org/10.3390/photonics9060423

[14] W. Sha, Ph.D. thesis (1992) at the University of Michigan, Femtosecond lasers and applications to ultrafast semiconductor transport and THz generation and detection.

[15] T. Norris, T. Sizer II, and G. Mourou, Generation of 85-fsec pulses by synchronous pumping of a colliding-pulse mode-locked dye laser, Journal of the Optical Society of America B Vol. 2, Issue 4, pp. 613-615 (1985)

[16] G. Chang, Z. Wei, Ultrafast Fiber Lasers: An Expanding Versatile Toolbox. iScience, Volume 23, Issue 5, 22 May 2020, 101101

[17] For example, see NKT white paper, available online: https://www.nktphotonics.com/wp-content/uploads/2022/01/modal-properties-of-dc-200-40-pz-yb-updated.pdf; www.nktphotonics.com and references therein.

[18] G. Mourou, B. Brocklesby, T. Tajima, and J. Limpert, The future is fibre accelerators, Nature Photonics 7, 258 (2013).

[19] J.-C. Chanteloup, S. Bellanger, L. Daniault, I. Fsaifes, M. Veinhard, J. Bourderionnet, C. Larat, E. Lallier et A. Brignon, Shaping the light: The advent of digital lasers, Laser Focus World, Vol. 57, No. 6, June 2021. https://www.laserfocusworld.com/lasers-sources/article/14201008/shaping-the-light-the-advent-of-digital-lasers

[20] D. Du, X. Liu, G. Korn, J. Squier, and G. Mourou, Laser-induced breakdown by impact ionization in SiO2 with pulse widths from 7 ns to 150 fs, Appl. Phys. Lett. 64 (23), 1994

[21] D. Du and T. Juiraz, Femtosecond and Ophthalmology, presentations at the Symposium LUMIÈRE ET LASER À SAINT-MARTIN DE PALLIÈRES

[22] IntraLase FS Laser Operator's Manual, system specifications

[23] For examples, product catalog of Coherent, NKT Photonics, Spectra Physics, IPG, Trumpf.

[24] P. Russell, Photonic crystal fibers, Science 299(5605), 358–362 (2003) and references therein. NKT white paper, available online: https://www.nktphotonics.com/wp-content/uploads/2022/01/modal-properties-of-dc-200-40-pz-yb-updated.pdf

[25] D. Payne, Fiber amplifiers and the birth of internet, presentation and discussions of hollow-core fibers at the Symposium LUMIÈRE ET LASER À SAINT-MARTIN DE PALLIÈRES.

[26a] B. Wedel and M. Funck, Industrial fiber beam delivery enhances ultrafast laser machining, Industrial Laser Solutions, 31, 1, 28–30 (Jan/Feb 2016); www.photonic-tools.de, product catalog.

[26b] A. Rudolf, Discussions of PT Photonics Tools in SPIE Photonics West (January 2025).

[26c] A. LEKOSIOTIS, F. BELLI, C. BRAHMS, M. SABBAH, E. SAKR, I. DAVIDSON, F. POLETTI, and J. TRAVERS, On-target delivery of intense ultrafast laser pulses through hollow-core anti-resonant fibers.

[27] S. Eilzer and B. Wedel, Hollow Core Optical Fibers for Industrial Ultra Short Pulse Laser Beam Delivery Applications, Fibers 2018, 6, 80; doi:10.3390/fib6040080

[28] J. Yang, S. Gurung, S. Bej, P. Ni. H. W. Lee, "Active Optical Metasurfaces: A Comprehensive Review on Physics, Mechanisms, and Prospective Applications," Reports on Progress in Physics 85, 036101 (2022)

[29] T. Tajima and P. Chen, eds. Progress of Laser Accelerator and Future Prospect**s** (MDPI, Basel, 2023), www.mdpi.com/journal/photonics/special_issues/Laser_Accelerator

[30] Verin V, Popowski Y, de Bruyne B, Baumgart D, Sauerwein W, Lins M, Kovacs G, Thomas M, Calman F, Disco C, Serruys PW, Wijns W; Dose-Finding Study Group., N Engl J Med. , (2001)344, 243. doi: 10.1056/NEJM200101253440401.PMID: 11172150 .

[31] Bernardi G., Ital Heart J Suppl. (2001)2, 559.

[32] Geiger MH, Ludwig J, Burckhard R, Scheinert D, Müller RG, Daniel WG, Sauer R, Strnad V.Strahlenther , Onkol. 2006, 182, 9. doi: 10.1007/s00066-006-1434-y.PMID: 16404515

[33] Fu DG., Cell Biochem Biophys. (2015) 73, 291.. doi: 10.1007/s12013-015-0626-4.PMID: 25737133

[34] Krug D, Blanck O, Dunst J, Bonnemeier H., Trends Cardiovasc Med. (2022) 32, 297-298. doi: 10.1016/j.tcm.2021.05.002.

[35] Wang S, Luo H, Mao T, Xiang C, Hu H, Zhao J, Wang X, Wang J, Liu H, Yu L, Jiang H., Heart Rhythm. (2023) 20, 1327. doi: 10.1016/j.hrthm.2023.04.052.

[36] Wielopolski PA, van Geuns RJ, de Feyter PJ, Oudkerk , M.Eur Radiol. (1998) 8, 873. doi: 10.1007/s003300050484.

[37] Beneš V, Bubeníková A, Skalický P, Bradáč O. Adv Tech Stand Neurosurg. (2024) 49, 139. doi: 10.1007/978-3-031-42398-7_8.

[38] Torazawa S, Miyawaki S, Shinya Y, Kawashima M, Hasegawa H, Dofuku S, Uchikawa H, Kin T, Shin M, Nakatomi H, Saito N. World Neurosurg. (2020) 140, 276. doi: 10.1016/j.wneu.2020.05.068.

[39] Erickson N, Mooney J, Salehani A, Thomas E, Ilyas A, Rahm S, Maleknia P, Yousuf O, Fiveash J, Dobelbower C, Fisher WS., 3rd.World Neurosurg. (2022) 160, 529. doi: 10.1016/j.wneu.2022.01.060.

[40] Boyer D, Hu A, Warrow D, Xavier S, Gonzalez V, Lad E, Rosen RB, Do D, Schneiderman T, Ho A, Munk MR, Jaffe G, Tedford SE, Croissant CL, Walker M, Rückert R, Tedford CE., Retina (2024) 44, 487. doi: 10.1097/IAE.0000000000003980.

[41] Neffendorf JE, Jackson TL. Clin Ophthalmol. (2015) 9, 1829. . doi: 10.2147/OPTH.S75638.

[42] Evans JR, Igwe C, Jackson TL, Chong V.Cochrane Database Syst Rev. (2020) 8(8). CD004004. doi: 10.1002/14651858.CD004004.pub4.

[43] Aitken KL, Hawkins MA.Clin Oncol (R Coll Radiol) (2015) 27, 307. doi: 10.1016/j.clon.2015.01.032.

[44] Malik U, Mohiuddin M. Semin Oncol. (2002) 29, 196. doi: 10.1053/sonc.2002.31675.

[45] Barry A, Wong R, Dawson LA. Int J Radiat Oncol Biol Phys. (2019) 103, 540. doi: 10.1016/j.ijrobp.2018.10.010.PMID: 30722966 No abstract available.

[46] Elaimy AL, Cao Y, Lawrence TS. Cancer J. (2023) 29, 266. doi: 10.1097/PPO.0000000000000679.

[47] Chino F, Stephens SJ, Choi SS, Marin D, Kim CY, Morse MA, Godfrey DJ, Czito BG, Willett CG, Palta M. Cancer. (2018) 124, 3476. . doi: 10.1002/cncr.31334.

[48] McPartlin AJ, Dawson LA. Cancer J. (2016) 22, 296. doi: 10.1097/PPO.0000000000000201.

[48-1] Cuculich PS, Schill MR, Kashani R, et al. Noninvasive Cardiac Radiation for Ablation of Ventricular Tachycardia. N Engl J Med. 2017 Dec 14;377(24):2325-2336.

[48-2] Stevenson WG, Wilber DJ, Natale A, et al. Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial. Circulation. 2008 Dec 16;118(25):2773-82.

[48-3] Dinov B, Fiedler L, Schönbauer R, et al. Outcomes in catheter ablation of ventricular tachycardia in dilated nonischemic cardiomyopathy compared with ischemic cardiomyopathy. Circulation. 2014 Feb 18;129(7):728-36.

[48-4] Robinson CG, Samson PP, Moore KMS, et al. Phase I/II Trial of Electrophysiology-Guided Noninvasive Cardiac Radioablation for Ventricular Tachycardia. Circulation. 2019 Jan 15;139(3):313-321.

[48-5] ClinicalTrials.gov Identifier: NCT05273697. Radiosurgical Ablation of Ventricular Tachycardia (RADIATE-VT) trial.

[48-6] Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370:1393-401.

[48-7] Böhm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications. Lancet. 2020 Apr 11;395(10231):1444-1451.

[48-8] RADIANCE-HTN Investigators. Endovascular ultrasound renal denervation to treat hypertension. Lancet. 2018;391:2335-45.

[48-9] Cai X, Yang Y, Shen Y, et al. Noninvasive Stereotactic Radiotherapy for Renal Denervation in a Swine Model. J Am Coll Cardiol. 2019 Oct 1;74(13):1697-1709.

[49] K. Svendsen, et al., Sci. Rpt. 11, 5844 (2021).

[50] A. Giulietti, et al., Phys. Rev. Lett. **101**, 105002 (2008).

[51] G. Grittani et al. patent applied (2016).

[52] F. Albert, et al., Plas. Phys. Contr. Fus. **56**, 084015 (2014).

[53] A. Hussein, et a., Sci. Rpt. **9,** 3249 (2019).

[54] J. Kieffer, et al., Proc. SPIE 12582, Compact Radiation Sources from EUV to Gamma-rays: Development and Applications, 1258206 (8 June 2023).