Development and application of compact and on-chip electron linear accelerators for dynamic tracking cancer therapy and DNA damage/repair analysis

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Abstract. We are developing compact electron linear accelerators (hereafter linac) with high RF (Radio Frequency) frequency (9.3 GHz, wavelength 32.3 mm) of X-band and applying to medicine and non-destructive testing. Especially, potable 950 keV and 3.95 MeV linac X-ray sources have been developed for on-site transmission testing at several industrial plants and civil infrastructures including bridges. 6 MeV linac have been made for pinpoint X-ray dynamic tracking cancer therapy. The length of the accelerating tube is ~600 mm. The electron beam size at the X-ray target is less than 1 mm and X-ray spot size at the cancer is less than 3 mm. Several hardware and software are under construction for dynamic tracking therapy for moving lung cancer. Moreover, as an ultimate compact linac, we are designing and manufacturing a laser dielectric linac of ~1 MeV with Yr fiber laser (283 THz, wavelength 1.06 μm). Since the wavelength is 1.06 μm, the length of one accelerating structure is tens μm and the electron beam size is in sub-micro meter. Since the sizes of cell and nuclear are about 10 and 1 μm, respectively, we plan to use this “On-chip” linac for radiation-induced DNA damage/repair analysis. We are thinking a system where DNA in a nucleus of cell is hit by ~1 μm electron or X-ray beam and observe its repair by proteins and enzymes in live cells in-situ.

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We try to apply this device to analyses of low dose radiation biological effect, especially Fukushima residents, and radiation sensitivity. Finally, we try to combine the pinpoint radiation therapy and radiation sensitivity analysis forward “Tailor-made Radiation Therapy”.

1. Introduction

As the aging society proceeds, cancer becomes most fatal disease. Radiation therapy is covering one third of the total modality of the therapy with surgery and chemical treatment. In addition to IMRT (Intensity Modulated Radiation Therapy) and particle beam therapy (proton and carbon), pinpoint X-ray dynamic tracking therapy is now under development. Small moving lung cancer can be diagnosed in situ by keV X-ray camera and tracked by a moving linac X-ray source. For the purpose, the accelerating structure of linac should be small by using higher resonant RF such as X-band (9.3 GHz) and C-band (5.712 GHz) comparing with S-band (2.856 GHz) large structure for IMRT. We are developing and openly use advanced S-band, X-band and laser electron linacs at University of Tokyo as shown in Figure 1. Especially, potable 950 keV and 3.95 MeV linac X-ray sources have been developed for on-site transmission testing at several industrial plants and civil infrastructures including bridges. 6 MeV linac have been made for pinpoint X-ray dynamic tracking cancer therapy [1]. We have been investigating X-ray assisted Drug Delivery Systems (DDS) with Cisplatin-micelle [2] and gold-nanoparticle-PEG (polyethylene glycol) [3]. Furthermore, we are designing and manufacturing a laser dielectric accelerator (hereafter, DLA) of ~1 MeV with Yr fiber laser (283 THz, wavelength 1.06 μm). Since the wavelength is 1.06 μm, the length of one accelerating structure is tens μm and the electron beam size is less than 1 μm. Since the sizes of cell and nucleus are about 10 and 1 μm, respectively, we plan to use this “On-chip” linac for radiation-induced DNA damage/repair analysis. We are thinking a system where DNA in a nuclear is hit by ~1 μm electron or X-ray beam and observe its repair by proteins and enzymes in live cells in-situ. We try to apply this device to analyses of low dose radiation biological effect and radiation sensitivity. Finally, we try to combine the pinpoint radiation therapy and radiation sensitivity analysis forward “Tailor-made Radiation Therapy”.

![S-band (2.856 GHz) Linear Accelerators](image1.png)

![Please second Time-resolved Linac-Laser Synchronization System for Radiation Chemistry](image2.png)

![Compact/Portable X-band(9.311.424GHz) Linac X-ray Sources for Medicine and NDT](image3.png)

![Laser Acceleration](image4.png)

Fig.1 Staged development of advanced electron linacs at University of Tokyo
2. RF frequency and size of medical linac
Accelerating structures of S-band (2.856GHz, wavelength 105 mm), C-band (5.712GHz, 50.3 mm) and X-band (9.3GHz, 32.3 mm) linacs and cancer therapy systems using them are depicted in Figure 2 in order to explain the dependence of the size of the medical device on the accelerating RF frequency. As the RF frequency is higher, it becomes smaller so that it can be installed in the smaller moving cases. S-band linac is widely adopted for conformational RT and IMRT. X-band and C-band linacs are adopted for stereotactic RT such as Cyberknife and dynamic tracking therapy due to their compactness recently (see Figure 2).

![Figure 2. S-band (2.856GHz), C-band (5.712GHz), X-band (9.3GHz) accelerating structures and cancer therapy systems](image)

3. 6 MeV medical system for dynamic tracking cancer therapy
We have developed an accelerating system capable of generating finer X-ray beams with 1mm X-ray spot size at cancers. In this system, we adopt beam scanning by controlled electric field in addition to mechanical scanning to achieve more rapid formation of radiation fields. We also aim at irradiating cancers with the X-rays from any direction in a three-dimensional space instead of on a two-dimensional plane. Accuthera CO., University of Tokyo, Hokkaido University and the National Cancer Institute are carrying out several research- and development-project under the NEDO (New Energy and Industrial Technology Development Organization) national project in Japan [4]. This project includes an X-ray micro-beam-accelerating system with the electromagnetic rapid scanning. Early cancers of 1-cm or less in diameter are the targets as well as cancers of 1-5 cm or less in diameter. This is equivalent to the practical stereotactic radiotherapy. Moreover, the dynamic tracking therapy in order to reduce irradiation dose against surrounding normal organs is available. Figure 3 shows the first 6 MeV machine for just a beam test and the fast X-Ray micro beam scanning system and a multi-axial robotic radiation and control system. Recently, we are developing an on-line MeV X-ray treatment-beam diagnostic device for safety as shown in Figure 4. We adopt the glass GEM (Glass Gas Electron Multiplier) [5,6,7] sensor which can realize both position- and dose-monitors. Position and movement of lung cancer are observed by two sets of 50 keV X-ray tubes and flat-panels.
In order to improve the accuracy and safety of pinpoint irradiation to a moving lung cancer, we are also constructing the position/image prediction software (see Figure 5). Here we make use of MSSA (Multi-Channel Singular Spectrum Analysis) method [8] to predict future information from past ones. This method rationally picks up dominant singular aspects from the data in the past, which is understood to be more reliable and faster than Fourier Transform Analysis. This can predict the motion of the centre-of-mass of a cancer in a projected plain (see (a) of Figure 5) [9]. Even the 2-dimensional image can be predicted as shown in (b) of the figure. Those image predictions would be very helpful at the monitoring screen [10]. Further, we are developing the dose calculation by the Boltzmann transport equation [11,12,13]. Pencil beam approximation where the dose distribution uses a certain modelling is widely used for its rapid calculation [14]. However, the accuracy is limited. On the other hand, Monte Carlo method can give most physically accurate distribution while it takes a lot of time. Thus, it cannot be used clinically yet. The Boltzmann scheme is rationally intermediate with acceptable accuracy and reasonable speed. We are developing our original on-line dose calculation system for the pinpoint X-ray dynamic tracking devise. We are going to apply the governmental permission in Japan and USA.
4. **On-chip µm electron/X-ray source for DNA damage/repair analysis**

We introduce updated DNA-radiation damage/repair observation and sensitivity analysis under collaboration with NIRS (National Institute for Radiological Science) and Tohoku University. We plan to investigate the radiation sensitivity of individuals and relate it to radiation cancer therapy. This may be able to contribute to “Taylor-made” radiation therapy. We use HIMAC (Heavy Ion Medical Accelerator in Chiba) and irradiate cells by carbon beams and others. HIMAC and irradiation facility are shown in Figure 6. Updated example is given in Figure 7. We irradiate 1BR-hTERT (human fibroblast) cells by Fe ions of 500 MeV/nucleon at a dose of 1Gy. DSB (Double Strand Break) is visible by accumulation of RPA repair proteins at the DSB sites in blue-dyed nucleus. Moreover, the cell cycle is also visualized by cell cycle marker, Cyclin B antibody which indicates S and G2 phases. Now, we are investigating the difference of DNA damage/repair on radiations such as ions (C, Fe, etc.), proton and X-rays. However, the cells are not living so that the on-line observation is not available yet. Micro ion beams less than 1 µm and even single ion are used for the single shot irradiation to cells and the bystander effect is studied. However, those ions are generated by using big accelerators such as cyclotron, very narrow collimator and low intensity operation. Therefore, the positions of such beams are still random within a few µm² area. It is impossible to hit a targeted position in a cell.

On the other hand, on-line time-resolved DNA-UV laser damage/repair observation with live cells is available at Prof. Akira Yasui’s laboratory of Tohoku University [15]. Here, 1 µm spot and 1 µm thick line of UV laser are spatially controlled and irradiation to cells and nuclei. Figure 8 and 9 show the irradiation and scanning system, and an example of the live cell imaging. Accumulation and disappearance of GFP-tagged XRCC1, single strand break marker in this study, are observed after 405nm laser irradiation with photosensitizer in U2OS cell.

In order to realize on-line time-resolved DNA damage/repair visualization system for live cells, we are designing and developing an on-chip sub-micron beam source. Figure 10 depicts that the accelerating structure becomes smaller for higher RF frequency. As an ultimate case, we adopts Yr fiber laser of 1.06 µm wavelength and 283 THz and one cell of its resonant structure becomes about 1 µm. We consider a set of comb shaped structure where two laser pulses are injected from the both sides as shown in Figure 10. The structure is made of dielectric material such as Silica glass. This kind of structure and application to beam acceleration are called photonic crystal [16] and DLA (Dielectric Laser Accelerator) [17]. The wavelength of light (λ) in a dielectric material of refraction index of n becomes λ/n. Therefore, the phase of light in the mid plane of the comb structure can be controlled by changing the depth and longitudinal length. It is known that the transverse electric field cannot accelerate a charged particle. However, we can design the optical phase in the mid plane so that an
electron beam can be continuously accelerated in the longitudinal direction by applying such a comb-shaped dielectric structure. We are designing to manufacture microscopically an electron gun, several DLA structures, Yr fiber laser (283 THz, wavelength 1.06 µm) and X-ray target on one chip. Schematic configuration, the laser under development and the future image of the whole device are depicted in Figure 11. The whole device would be table-top which is equivalent to the UV laser system in Figure 8. We plan to accelerate the electrons up to ~1 MeV and the spot size and intensity of converted X-rays are ~ 1 µm and ~10⁵ Bq. The intensity is similar to those of standard shielded radioisotopes so that it can be used even out of radiation controlled areas following a certain radiation safety regulation.

Figure 6 Cell irradiation system of HIMAC of NIRS, Japan

Figure 7 Visualization of DSB (Double Strand Break) and cell cycle
Figure 8 On-line observation system of DNA damage/repair by UV laser and optical microscopy (Prof. Akira Yasui, Tohoku University)

(a) 20 sec after irradiation  (b) 200 sec  (c) Irradiation and scanning system

Figure 9 On-line observation of DNA damage/repair by UV laser. Irradiation is done by 405nm laser 30 scans with photosensitizer, and the scanning is done by 488nm laser, by 20sec interval x10 times, and U2OS (human osteosarcoma) cells transfected by GFP-XRCC1 (Single strand break marker) are used.

Figure 10 Schematic configuration of the regular structure of the laser dielectric accelerator
5. Concluding remarks
We have successfully developed the X-band electron linacs for medicine and non-destructive testing. Especially, the 6 MeV linac is used for pinpoint X-ray dynamic tracking cancer therapy. The length of the accelerating structure is ~600 mm. The electron beam size at the X-ray target is less than 1 mm and X-ray spot size at the cancer is less than 3 mm. Several hardware and software are under construction for dynamic tracking therapy for moving lung cancer. Moreover, as an ultimate compact linac, we are designing and manufacturing the “On-chip” ~1 MeV DLA with table-top Yr fiber laser. We plan to use this DLA for radiation-induced DNA damage/repair analysis. We try to apply this table-top device to analyses of low dose radiation biological effect, especially for Fukushima residents, and radiation sensitivity. Finally, we try to combine the pinpoint radiation therapy and radiation sensitivity analysis forward “Tailor-made Radiation Therapy”.

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