Futuristic Trends in Radiation Oncology

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ABSTRACT

Radiation oncology- the branch of medicine that treats cancer by use of ionizing radiations, is an ever-evolving subject. Rapid technological advancements and expansion of scientific knowledge on biology of cancer has brought forth many exciting new techniques in radiotherapy. Here we discuss about three such promising latest advances in the field of radiation oncology. Firstly, we elaborate on MR-LINAC, that integrates Magnetic Resonance Imaging with a medical Linear Accelerator for therapeutic purpose- that enables better adaptation of radiation delivery with change in patient's anatomy as well as tumor response during treatment. Next, we briefly highlight on FLASH radiotherapy- another novel radiation technique that is still investigational clinically. This technique that uses ultra-high dose rates for radiation delivery, may be a potential game changer to overcome tumor radioresistance. Lastly, we discuss the upcoming technique of Lattice radiation therapy that aims to redefine the conventional norms of dose prescription and distribution for photon beam treatments. These techniques warrant further clinical research and constitute the latest advancements in the field of radiotherapy.

Keywords: Radiotherapy, Radiation oncology, MR-LINAC, FLASH radiotherapy, Lattice radiotherapy, Recent advances

I. INTRODUCTION

Radiation Oncology is that discipline of human medicine which deals with the generation, conservation and dissemination of knowledge related to causes, prevention and treatment of cancer, involving special expertise in therapeutic applications of ionizing radiation. Radiation oncology is one of the earliest developed branches in the multidisciplinary management of cancer. Since the discovery of X-rays by Wilhelm Conrad Roentgen in 1895, this branch has integrated itself with technological advancements and evolved successfully. The primary principle of radiotherapy is to deliver a specific dose of radiation to a defined tumor volume with minimum damage to surrounding tissues. The modern-day equipment and incorporation of computer technology in radiotherapy ensure accurate three-dimensional image-based tumor delineation and treatment planning with more precise delivery of radiation therapy. Teletherapy has now moved on from Cobalt-60 gamma sources to utilization of high energy x-rays photons produced by complex Linear Accelerators (LINACs). The LINACs themselves have undergone many makeovers in order to improve precision. The latest LINACs are equipped with improved versions of Multi-Leaf Collimators in their treatment heads which enable sophisticated radiation treatment delivery in the forms of Intensity Modulated Radiotherapy (IMRT), Volumetric Modulated Arc Therapy (VMAT), Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiotherapy (SBRT). Furthermore, they are integrated with onboard imaging devices that can detect and measure daily variations in the patient's anatomy or tumor topography during the course of fractionated radiotherapy treatment- called Image Guided Adaptive Radiotherapy [1]. Robotic LINACs with accurate image guidance and sub-millimetre precision have been developed, known as CyberKnife [2]. Most recently, Particle beam therapy with protons or heavier ions like carbon-ion has been added as a new mode for radiation delivery. This has become an attractive option as Protons spare healthy surrounding normal tissues from side effects of radiation more effectively than conventional photon therapy [3,4].

In this chapter, we will briefly highlight three new radiation therapy modalities that are in their nascent stages and have been in clinical use only since the last decade. They are the Magnetic Resonance-LINAC (MR-LINAC), FLASH radiotherapy and Lattice radiotherapy techniques. They are the future of Radiation Oncology and have the potential to change the entire landscape of this field.

II. FUTURISTIC TRENDS IN RADIATION ONCOLOGY

A. MR-LINAC

MR-LINAC is a fully integrated system utilizing magnetic resonance imaging (MRI) together with a Linear accelerator technology to treat cancers across the human body. This means the system can deliver treatment photon beams to the radiation target volume while simultaneously monitoring the area with a high soft tissue resolution. The MR-LINAC systems currently available are the 0.35 Tesla ViewRay MRIdian system and the 1.5 Tesla Elekta Unity system [5,6]. Most recently, the Unity MR-LINAC has been developed by the University Medical Center, Utrecht, in collaboration with Elekta AB (Stockholm, Sweden) and Philips (Best, The Netherlands). It integrates a 1.5 Tesla MR-imaging scanner with a radiotherapy linear accelerator and was clinically introduced for the treatment of oligometastatic lymph nodes for the first time in 2018 [7-9].

This technology revolutionizes radiotherapy treatment by enabling soft-tissue contrast MR imaging directly from the treatment table to visualize all anatomical changes occurring during radiotherapy. The variations can be detected in between fractions on a daily basis (inter-fraction motion) as well as during the delivery of one particular radiotherapy fraction (intra-fraction motion) [10]. Utilizing the information, corrective measures can be applied immediately before the treatment delivery with the patient still on the LINAC couch (real-time replanning), or the patient may be subjected once again to the entire process of simulation and radiotherapy planning which is then tailored to the changing tumor topography (adaptive radiotherapy) [11]. This would lead to better conformality and accuracy in radiation delivery to tumors while concomitantly lowering normal tissue side effects. The anatomical and functional MRI sequences obtained on the LINAC can also help in real-time treatment response assessment [12-13].

A workflow of the MR-LINAC system is shown in Figure 1. Plan adaptation can be divided into two main categories in MR-LINAC: 'adapt-to-position' (ATP) and 'adapt-to-shape' (ATS). In the ATP adaptive method, the pre-treatment CT scan is matched with the online MRI through rigid registration, followed by re-optimization on the treatment isocenter to improve target coverage. Thus, no new contours are generated for the adapted plan in this method. In contrast, the ATS adaptive method is based on the variations in the patient's anatomy during the course of treatment and the plan is optimized on daily MRI and adapted contours.

There are currently several limitations towards the widespread use of this emerging technology. It comes with a high capital cost over a conventional LINAC in terms of equipment, infrastructure, quality assurance and training. Also there will be a learning curve to seamlessly transition MR-LINAC for routine clinical use. It can be

expected that with increased clinical experience and generation of Phase III data, the utility of MR-LINAC will be established across all types and sites of cancer in the near future.

B. FLASH RADIOTHERAPY

The term "FLASH" radiotherapy was first coined in 2014 by Favaudon et al [14]. In FLASH radiotherapy, radiation dose to a tumour is delivered at ultra-high dose rates (>40 Gray/second) as compared to conventional dose rates (approximately 5 Gray/min). This results in increased normal tissue sparing from radiation-induced toxicities- a phenomenon called the "FLASH effect" [15]. The earliest report on the advantages of ultra-high dose rate irradiation and the FLASH effect on in vivo mice models was published in 1966 [16]. With the advances in radiotherapy technology opening the prospects of using it clinically, there has been a renewed interest in it recently. Several preclinical trials on mice, mini-pigs and cats have demonstrated the normal tissue sparing capability while maintaining tumor control by FLASH radiotherapy compared to conventional radiotherapy [14,17,18]. This opens up the possibility of delivering large dose to radioresistant tumors with FLASH radiotherapy, as it promises a much higher therapeutic index. The first clinical treatment with FLASH irradiation was carried out in Laussane University Hospital in a case of recurrent T-cell cutaneous lymphoma in 2018 by Bourhis et al [19]. A 3.5 cm tumor was treated with 15 Gy total dose of FLASH radiotherapy delivered in pulses. Ten pulses of 1 microsecond each were used at a dose rate greater than 10^6 Gy/second, delivering 1.5 Gy per pulse over a total treatment time of 90 milliseconds. A complete clinical response was seen at 36 days, and the normal tissue toxicities the patient experienced were milder and also healed quicker as compared to his previous radiotherapy treatments.

The radiobiology of the FLASH effect is yet to be fully understood. It is hypothesized that FLASH irradiation, due to its ultra-high dose rate and short treatment time, creates an environment of oxygen depletion in the irradiated tissue [20,21]. The local oxygen is depleted faster than time to reoxygenation, which leads to transient radiation-induced hypoxia and radioresistance in the normal tissues, thereby protecting them from effects of FLASH radiotherapy. Another theory is that FLASH irradiation induces contrasting radiobiology between normal and cancer cells due to the differences in redox chemistry and free radical production [22]. Normal tissue cells are presumed to have lower oxidative burdens during normal redox metabolism and an increased ability to sequester labile iron compared to cancerous cells- i.e., they more efficiently reduce the levels of free radicals and hydroperoxides generated from reactions following FLASH. This increases the oxidative burden in cancer cells, resulting in their cytotoxicity with sparing of surrounding normal tissues. The inflammatory and immune responses have also been attributed to FLASH effect- most notably the levels of pro-inflammatory cytokine: transforming growth factor - β (TGF-β) [23]. Reports of increased T-lymphocyte recruitment in tumor microenvironment following proton irradiation at FLASH dose rates further suggest the role of immune response contributing towards the FLASH effect [24].

The source of radiation that has been frequently used in the preclinical FLASH investigations and clinical use is electrons of 4-20 MeV energy range, generated from linear accelerators modified to match the physical parameters of the FLASH effect [15]. For treatment of deep-seated tumours, use of proton beam therapy (PBT) and heavy-ions (Carbon-ions) have been proposed [25,26]. Although theoretically, they offer a markedly improved therapeutic ratio with FLASH dose rates, there are huge technical limitations in using them for large tumor volume. At present there is no adequate technology for delivery and quality assurance of PBT- FLASH irradiation along with issues pertaining to radiation protection. It will require considerable research at both technological and clinical levels before FLASH radiotherapy can be offered to cancer patients routinely.

C. LATTICE RADIATION THERAPY

This is the latest technique of radiotherapy that aims to administer curative radiation doses inside tumors while simultaneously lowering doses to the adjacent organs at risks (OARs). The basic understanding and efforts in radiotherapy planning have historically been to improve the homogeneity of the radiation dose delivery- i.e. all parts of the tumor volume should receive a sufficiently equal curative dose. However, when high doses of radiation are required to cure a particular type of cancer, conventional RT cannot achieve dose homogeneity within the tumor without increasing radiation spillage to nearby OARs. This low dose radiation received by OARs in close proximity to tumors, eventually contribute to increased normal tissue toxicities. On the contrary, Lattice therapy aims to deliver focal high doses of radiation (vertices or hotspots) to discrete sub-volumes within the tumor while creating surrounding low dose areas (periphery)- resulting in a markedly heterogenous radiotherapy plan. This is achieved by delivering radiation beams from different directions at the tumor. The consequent alternating dose areas of spatially arranged peaks and valleys creates a three-dimensional array or matrix, unlike the two-dimensional dose distribution of a grid achieved with conventional RT (as shown in Figure 2). This technique is thought to be especially beneficial for treating larger lesions (greater than 5 cm) to very high doses

of RT. It is also postulated that the unique dose distribution of Lattice RT potentially modulates tumor microenvironment, thereby mounting a strong host immune response against the cancer cells [27].

Presently, most available clinical data with Lattice RT are case reports or case series and only a few clinical Phase I studies have been reported [28,29]. However, it has already been explored across various cancer sites ranging from lung to cervix to anal canal carcinomas as well as soft tissue sarcomas [30]. Literature suggests that Lattice RT can be delivered exclusively as a curative radiotherapy treatment in five fractions or as a non-exclusive hybrid radiotherapy, wherein, one to three Lattice RT fractions are followed by conventional RT. However, there is still a lot to be learnt about the ideal fractionation regimens and array design for dose prescription with regards to Lattice RT. Some literature suggest that a dose prescription based on 18-FDG PET scan data of the tumor to guide the localization of vertices would be optimum for Lattice RT, i.e. a metabolically guided approach [29]. Also, more research is required to evaluate the concurrent use of systemic therapies like chemotherapy and immunotherapy with Lattice RT. Yet, the early encouraging results of Phase I studies on efficacy and safety have prompted the initiation of a Phase II clinical trial with Lattice RT (NCT04553471) and the results are eagerly awaited.

III. CONCLUSION

Radiotherapy is an ever-evolving branch of medicin,e and with the rapid strides made in computer electronics and technology, it is also undergoing tremendous advancements. These are some, but not all, of the newest techniques that promises to revolutionize radiotherapy over the years to come. As medical professionals treating one of the leading cause of morbidity and mortality across the globe, we oncologists always keep an eye on the horizon to embrace the futuristic trends in patient care.

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FIGURES and LEGENDS

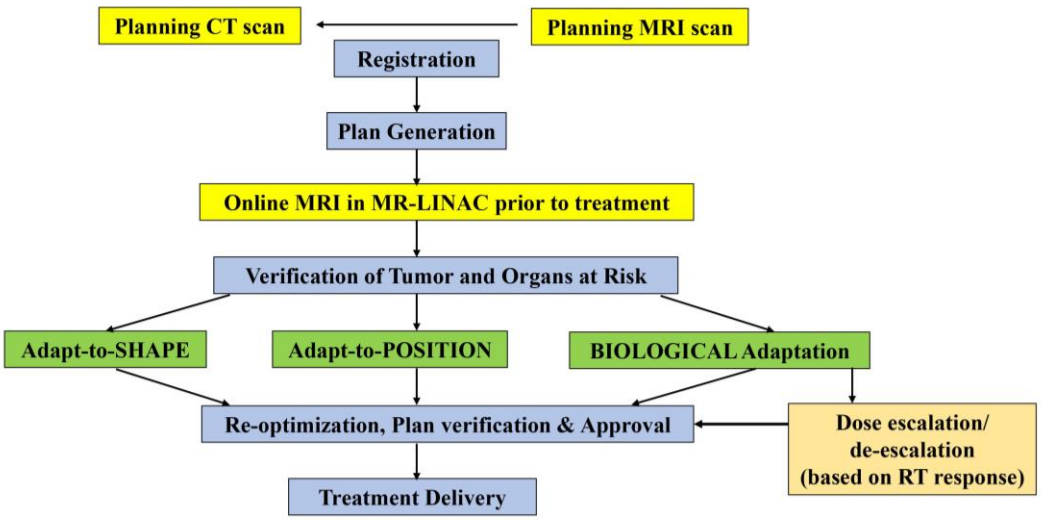

Figure 1: Workflow demonstrating the steps of Online Adaptive Radiotherapy in a MR-LINAC system

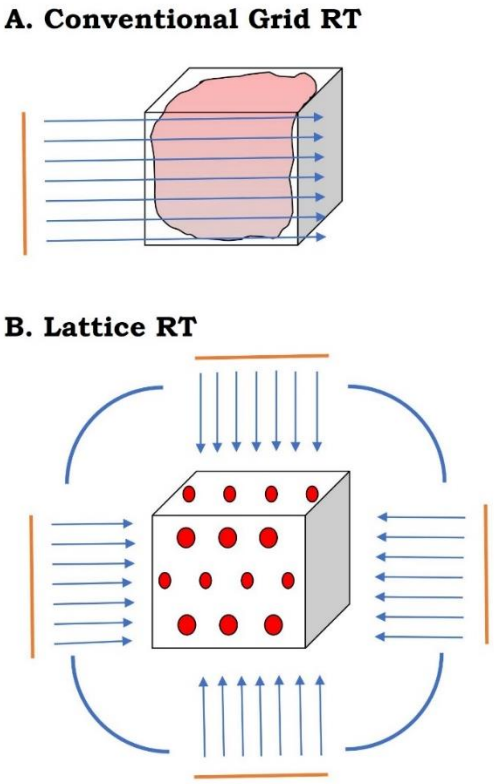

Figure2: A- The conventional grid radiotherapy uses a unidirectional parallel photon beam towards the target to deliver a homogenous dose distribution. B- In contrast, Lattice radiotherapy delivers the radiation in a multi-directional manner to create a three-dimensional array of alternating high and low dose areas (peaks and valleys) within the tumor volume.