RECENT ADVANCEMENTS IN RADIATION THERAPY FOR CANCER MANAGEMENT

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Introduction:

Radiation therapy is an essential therapeutic modality and forms an important component in the multimodal management of cancer treatment along with surgery, chemotherapy, targeted therapy, and immunotherapy. Radiation therapy involves treating malignant tumors (cancers) using ionizing radiation. Essentially, ionizing radiation is of two types, electromagnetic and particulate (heavy-ion) radiation.

Ionizing radiations can cause cellular damage through various mechanisms, however, the most lethal of them is the double-stranded DNA breaks that can occur by 1) Direct DNA damage- directly damages DNA produced by high LET radiations like protons and carbon ions.2) Indirect DNA damage caused by the low LET ionizing radiations like x-rays and electrons.

Clinically, radiation therapy has a curative role in certain cancers (Cervix, Prostate, Oropharynx, Nasopharynx, Lungs, etc), an adjuvant role after surgery (cancers of the Oral cavity, Breast, Brain, etc), neoadjuvant role before surgery to shrink the tumor, and palliative role (metastatic disease to alleviate symptoms like pain arising from large tumors or from large lesions in the bone, bleeding, spinal cord compression, etc). Radiotherapy can be used as a single modality or as a combinatorial therapy with chemotherapy, surgery, immunotherapy, hormone therapy, etc.[1,2]Although radiation therapy targets cancer cells, it also has a damaging effect on the surrounding/adjacent normal tissue that can lead to acute or sometimes late complications. Therefore, contemporary radiotherapeutic management aims to achieve effective tumor control probability or TCP (the probability of tumor cell kill within the defined target volume at a certain radiation dose) along with the reduction in normal tissue complication probability or NTCP (the probability that a certain percentage of the patient population will incur complications in the exposed normal tissue beyond a given threshold radiation dose. The ratio between TCP and NTCP is known as therapeutic ratio.

Clinically, radiotherapy is delivered to patients using external beam radiotherapy (EBRT), also called teletherapy and Brachytherapy (delivery of radiotherapy by putting the radio-

isotopes either within the tumor or in close proximity to the tumor). Conventionally, external radiation is delivered using photons (electromagnetic radiations like X-rays and gamma-rays) and electrons, that can penetrate through smaller depths and hence can be used for treating superficial malignancies that are in close proximity to the body surface. Deep-seated tumors can be effectively treated using particle radiation, such as proton and carbon ions, Particle beams, being high LET radiations, have higher penetrating power and relative biological effectiveness (RBE) resulting in more effective cell kill and better tumor cell eradication. Moreover, newer modalities like Intensity Modulated Proton Therapy (IMPT) in contemporary machines allow for a more targeted radiation delivery with a consequent reduction in normal tissue complications.

In the present era, External Beam Radiotherapy (EBRT) can be delivered by several approaches that include 3-dimensional conformal radiotherapy (3DCRT), Intensity-Modulated Radiotherapy (IMRT), Volumetric Modulated Arc Radiotherapy (VMAT), Image-Guided Radiotherapy (IGRT), Stereotactic Radiosurgery (SRS) for cranial tumors, Stereotactic Body Radiotherapy (SBRT) for extracranial tumors, protons and heavy ion therapy, etc.

Transition of Radiotherapy Delivery Techniques: 2-Dimensional to 3-Dimensional Techniques:

Radiation delivery techniques have evolved from 2-D technique to 3-D conformal RT (3DCRT) to IMRT/VMAT. Historically, when advanced radiotherapy planning was not available, EBRT was delivered by 2D technique in which rectangular fields based on plain orthogonal X-ray imaging. With the advent of advanced and sophisticated computing technology, it has now been possible to transition from 2-dimensional treatment planning and delivery (2-D radiotherapy) to a more sophisticated approach with 3-dimensional conformal radiotherapy (3-D CRT). The shift from the 2-D to 3-D conformal era has enabled to treat the tumor conformally and spare the normal tissue, thereby improving the therapeutic ratio.

3-Dimensional Conformal Radiotherapy is a form of EBRT that is based on 3-D anatomic information obtained from CT or MRI that conforms as closely as possible to the target volume in terms of tumoricidal dose to the tumor (target)and minimum possible dose to the adjacent normal tissue.3-Dconformal radiotherapy (CRT) is an improvement over 2-D RT as it uses CT or MR images instead of conventional orthogonal X-rays, allowing for accurate tumor and normal tissue delineation, facilitating optimal beam positioning thereby directing the beam towards the target and shaping the beam using multi-leaf collimators such that it conforms to the shape of the tumor and sparing the surrounding normal tissues (for e.g. tumors in close proximity to the kidneys, lungs, parotids or spinal cord).[3]

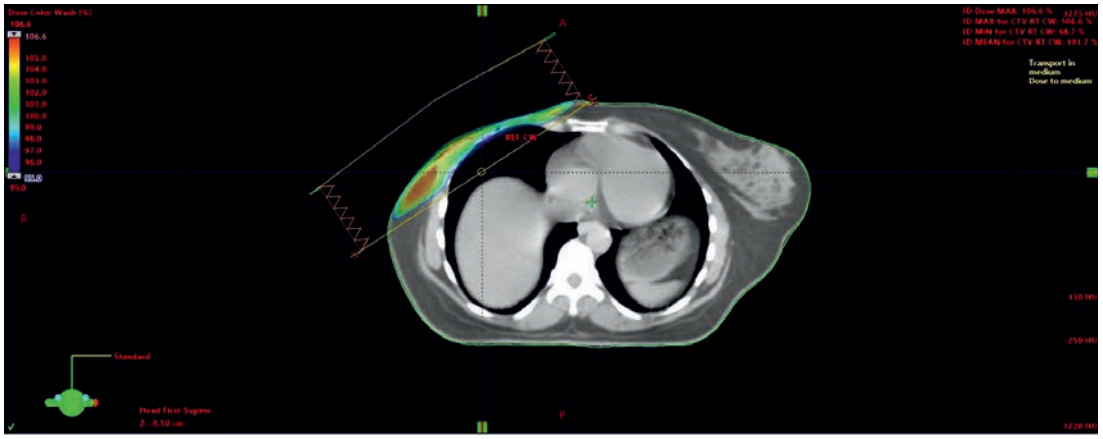

Figure 1- 3DCRT plan in a case of post-operative carcinoma breast.

Intensity Modulated Radiation Therapy (IMRT) is an innovative and sophisticated method to deliver a more conformal treatment where the beam intensity is modulated with computer-aided optimization to achieve a much superior dose distribution compared to the conventional 3-D conformal therapy. Although IMRT offers excellent precision and conformity, it is quite labor and resource-intensive and comes at a high cost, requiring complicated, time-consuming processes [dosimetry and treatment quality assessment (QA)]. Compared to 3-D conformal RT, IMRT has higher dose conformity indices which can result in geometrical errors.[4] However, this can be circumvented by a stringent quality assurance program that reduces these errors.

Volume-modulated arc therapy (VMAT) is a unique form of intensity-modulated radiation therapy (IMRT) that enables the patient to receive treatment from a full 360° beam angle by continuously rotating the radiation source. It combines the ability to achieve highly conformal dose distributions with highly efficient treatment delivery. This radiation technique permits simultaneous modification of three parameters, namely the speed of gantry rotation, the treatment aperture shape via movement of MLC leaves, and the dose rate allowing for better dose conformity and homogeneity within the target, resulting in reduced doses to the adjacent normal tissue. In this respect, VMAT is more effective than IMRT in sparing the organs at risk.[5]

Stereotactic Radiosurgery (SRS), Stereotactic body radiation therapy (SBRT), or stereotactic ablative radiotherapy (SABR) entails the precise and highly focused delivery of very high radiation doses in a small number of fractions resulting in ablation of the tumor. SRS is usually utilized to treat intracranial tumors like brain metastasis, small meningiomas, or acoustic schwannomas, while SBRT is commonly used for extracranial tumors, e.g., cancers of the lung, liver, pancreas, spine, etc. The high dose per fraction does not have a clear definition, but it is usually higher than 5Gy/faction. SBRT is considered to be highly conformal with a rapid dose gradient resulting in accurate treatment delivery to the tumour.[6]

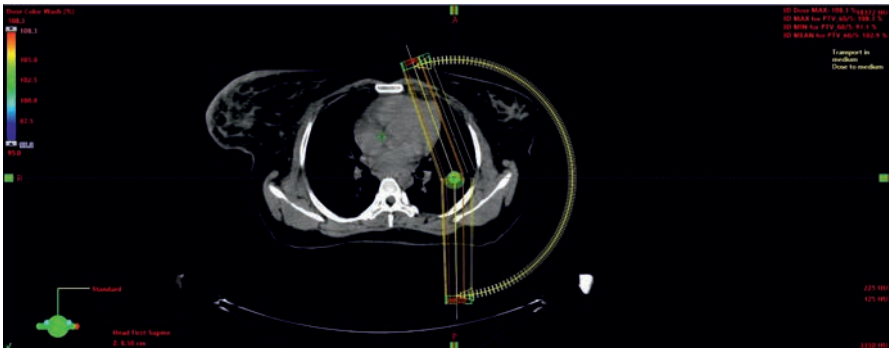

Figure 2- Stereotactic Body Radiotherapy (SBRT) Lung (60Gy/5 fractions)

FLASH Radiotherapy:

FLASH RT is the delivery of ultra-high dose rate of radiation (≥ 40 Gy/s) as compared to conventional radiotherapy where radiation doses are typically in the range of *vs*. 0.5–5 Gy/min

In FLASH radiotherapy (RT), the target is exposed to radiation at an extremely high dose rate. In comparison to conventional radiation therapy, FLASH-RT has been proven to lessen radiation-induced toxicity in healthy tissues without sacrificing the treatment's anti-cancer effects. This is called the Flash effect. Differences between normal and cancer cells' biological responses, particularly regarding radiation-induced rates of free radical elimination and decay, are thought to be the mechanism by which FLASH-RT reduces normal tissue toxicity, accounting for the positive therapeutic index of FLASH-RT.

The mechanism for FLASH therapy is yet to be elucidated, the most plausible hypothesis being “acute transient oxygen depletion” One of the assumptions of the mechanistic basis of FLASH radiotherapy is the Oxygen depletion hypothesis-Ultra-high dose rates cause normal tissues to reduce oxygen, which reduces the amount of indirect radiation-induced DNA damage and causes radio-resistance, which makes healthy tissues around the target more tolerant of radiation.[7] Instant oxygen depletion caused by FLASH-RT results in transient radiation-induced hypoxia. This is important because tumors consist of cell populations that are oxic, hypoxic, and anoxic, whereas normal tissues are often well-oxygenated and have a system in place to maintain their oxic state. Irradiation of tissues with FLASH-RT results in radiochemical oxygen depletion arising due to the reaction of oxygen with the free radicals, giving rise to an extremely acute period of hypoxia within the irradiated tissue and consequently a transient radio-resistance. This phenomenon is not seen with conventional RT as there is enough time for oxygen to permeate into the radiation-damaged area and replace the oxygen that was used to repair free radicals. This explains the reduced tissue toxicity with FLASH RT but does not clearly explain the equivalent tumoricidal effect as compared to conventional RT. Tumor tissue is supposed to have lower oxygen concentration (hypoxic) as compared to normal healthy tissue and therefore, the impact of FLASH RT on tumor radiosensitivity is minimal. Perhaps a decreased capacity for DNA repair relative to normal tissue makes up for the radio-resistance brought on by oxygen deprivation in tumor tissue.[8]

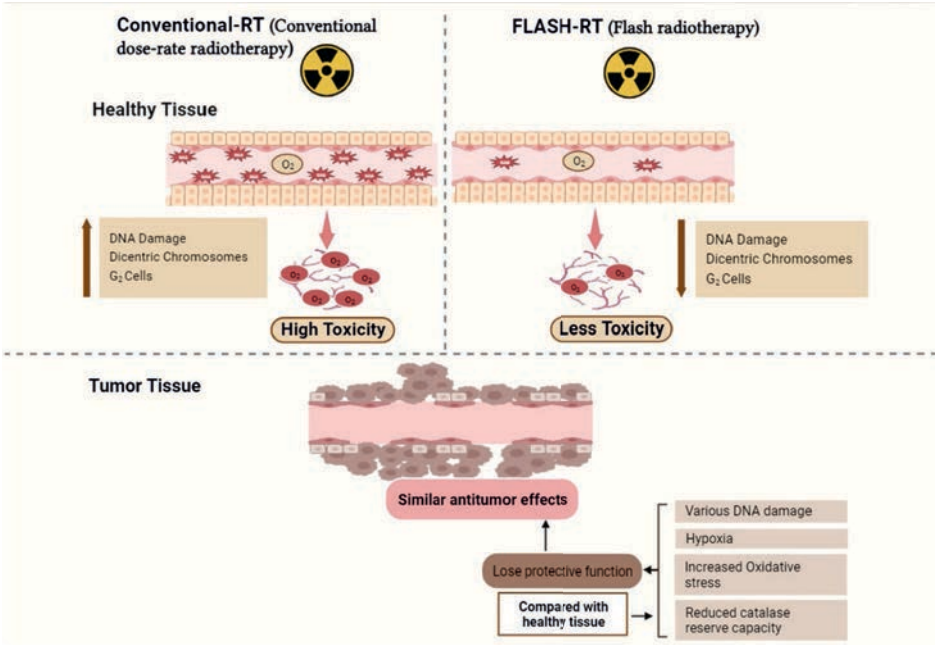

Figure 3- Biological mechanism of FLASH-RT.

Clinical utility and experience of FLASH RT

FLASH-RT can be indicated in two main clinical situations 1) For treating radioresistant tumors and 2) to minimize radiation-induced toxicity in tissues that are close to the target(tumor), in situations where large doses required for local tumour control would cause intolerable toxicity if administered using conventional radiotherapy technique. One of the first cases to be treated with FLASHRT was a multi-resistant cutaneous T-cell lymphoma of the skin, using 5.6MeV electron to a dose of 15Gy in 90ms. The treatment was well tolerated and the maximum toxicity that was observed was grade-1 skin toxicity with a complete response of the tumor. A phase-1 study (FAST01trial) from Cincinnati Cancer Centre enrolled 10 patients of bone metastasis for FLASH therapy and showed that FLASH therapy was safe and feasible.[9]

The advantages of FLASH RT are short treatment time (<0.1s), treatment delivery uncertainties caused by intrafraction motion are minimal, thus enabling for narrower treatment margins and lesser doses of radiation to be delivered to healthy tissue, equivalent tumor response as with conventional dose rates, minimal toxicities and can potentially achieve higher doses as compared to conventional RT due to its better therapeutic index.

Although FLASH RT has numerous advantages as mentioned above, there are still a few challenges for its adoption in routine clinics. One of the foremost challenges of FLASH RT is that its use is limited to superficial tumors, however, few studies have shown its clinical utility in deeper tumors like bone metastasis. Further clinical research is warranted to ascertain its use in deep-seated tumors. Secondly, the radiobiological explanation of FLASH therapy is yet to be fully understood and elucidated. Thirdly physical modifications in

existing LINACs to match physical parameters, rigorous quality assurance, and dosimetric verification are required to make this treatment modality an attractive treatment option. Lastly, the dose fractionation needs to be evolved for its routine clinical use.

HADRON THERAPY:

An important development in the field of radiation therapy delivery is the use of hadrons such as proton and carbon ions for treating cancer. Ideally, radiation therapy should give a uniform dose distribution within the target volume with minimal spillage outside. However, it is not possible to achieve the same clinically with the best available photon or X-ray-based therapies like IMRT. The next best thing is to deliver a tumoricidal dose to the target volume with a simultaneous reduction in radiation dose spill to the normal tissues adjacent to the tumor. By using hadrons, it is possible to achieve this dose distribution wherein the radiation dose is delivered uniformly across the target (tumor) with minimal spillage to the surrounding tissue. The advantage of protons over photons is because of their characteristic Bragg's peak (the sharp increase in the dose deposition at the end of the particle range).[10] Thus, by manipulating this physical property, particle therapy can yield better dose distributions than photon therapy, thereby providing a therapeutic ratio advantage[11]. This makes proton beams unique in therapeutic settings when used on patients, particularly pediatric and adult tumors that are in proximity to critical structures, such as the spinal cord and tumors at the base of the skull.[12,13]

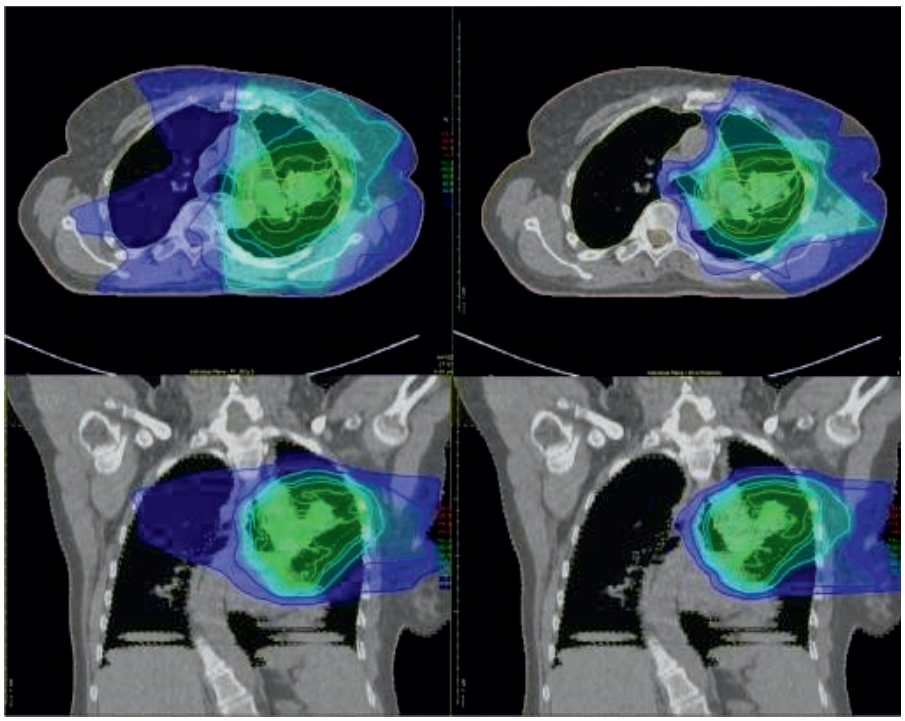

Figure 4- Comparison of the dose wash between photon and proton. The top panel shows the dose distribution of photons. The lower panel shows the dose distribution of the photons. (Adapted from Proton vs IMRT Lung)

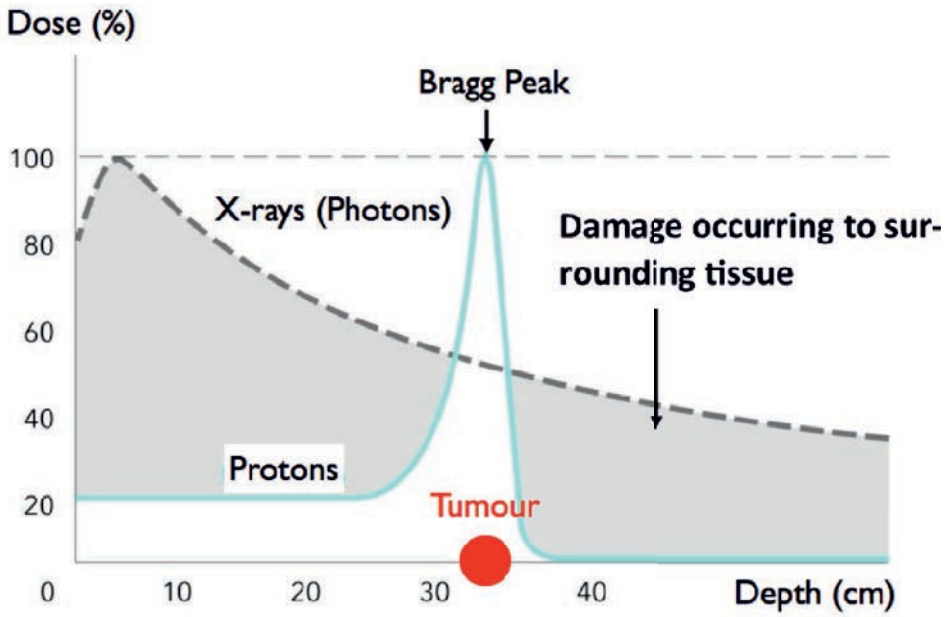

Figure 5- Graph showing Bragg's Peak of Protons (adapted from the potential of Proton therapy).

Protons are produced from the hydrogen obtained either from the electrolysis of deionized water or from commercially available high-purity hydrogen gas. Proton is introduced into the particle accelerator which is a series of electromagnets displacing ions and increasing their energy by increasing the velocity. Once the protons acquire a critical energy, they are introduced into the cyclotron or synchrotron. A single accelerator can provide proton beam in several treatment rooms by using bending magnets. Depending on the number of treatment rooms, the proton facility can vary in size. For shaping a particle beam, two techniques are commonly used:1) Beam Scattering technique.2) Beam Scanning technique.[10,14]

Radiobiologically, protons are known to generate more free radicals, resulting in increased apoptosis, immune response, decreased angiogenesis, reduced cell invasion/migration, and a possible increase in abscopal effect.[15]

Although, across the world, protons have been in clinical use for the last two decades, one of the chief concerns regarding clinical proton therapy is the lack of randomized clinical trials that generate level-1 evidence to show its superiority over photons. While dosimetric studies have clearly demonstrated their superiority in terms of dose conformity and homogeneity over photon therapy, the majority of the clinical evidence comes from phase-II clinical studies or retrospective studies.[16–20] Moreover, the cost of implementing proton therapy is quite high, so a cost-benefit analysis will give a more robust and pragmatic solution to patient therapeutic approach, especially in developing countries.[21]

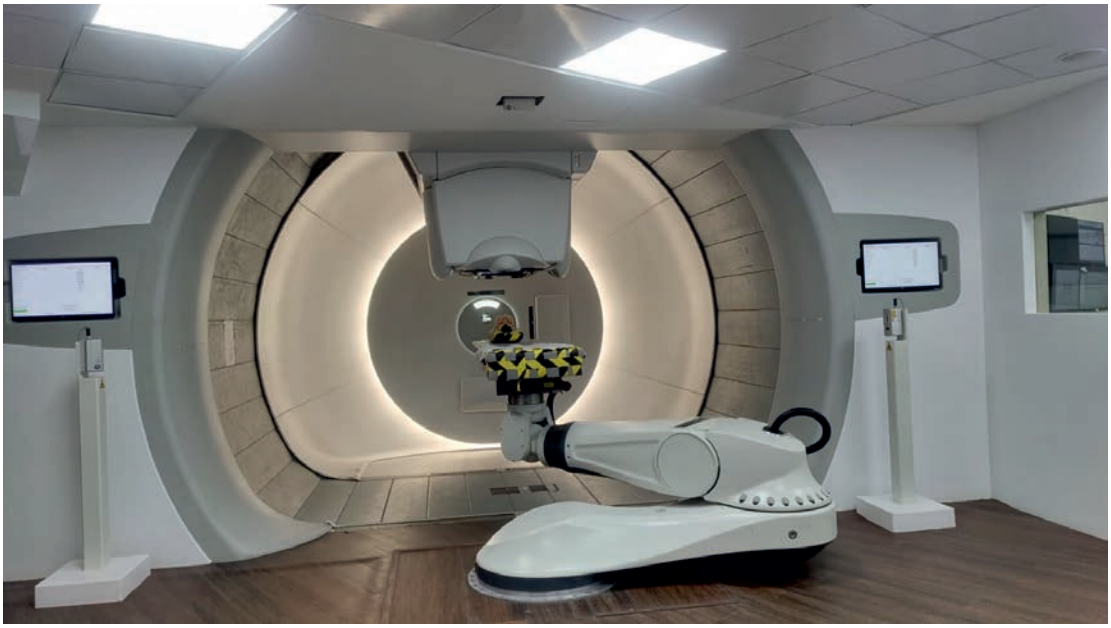

Figure 6- Proton therapy gantry at National Hadron Centre, Tata Memorial Centre India.

SFRT (Spatially Fractionated Stereotactic Body Radiation Therapy):

GRID therapy rechristened as Spatially Fractionated Stereotactic Body Radiation (SFRT), Therapy involves the delivery of heterogeneous doses to the entire tumor treating the tumor to tumoricidal doses while remaining within the threshold of the surrounding normal organ tolerance.[22]Itinvolves delivering relatively high but heterogeneous radiation dose to the tumor through a perforated screen with blocked areas called a GRID.[23] Unlike conventional radiation therapy, SFRT allows for radiotherapy dose escalation allowing delivery of high radiation doses akin to SRS/SBRT radiation dose levels particularly in large & bulky tumours, without causing any excessive damage to the adjacent normal tissues. As a result, SFRT allows for significantly higher doses to be tolerated by the skin and subcutaneous tissues. SFRT can be delivered by an innovative method called the 3D LATTICE Radiotherapy technique (LRT)in which the entire tumor volume is divided into a number of discrete, tiny spheres or vertices receiving very high radiation doses at the center of the target, simultaneously keeping lower dose levels at the periphery of the tumor in order to minimize the unwanted acute toxicities associated with high dose radiation therapy.[24] LRT is the 3-dimensional extension of the 2D GRID technique in which the vertices are encompassed within the gross tumor volume.[23]

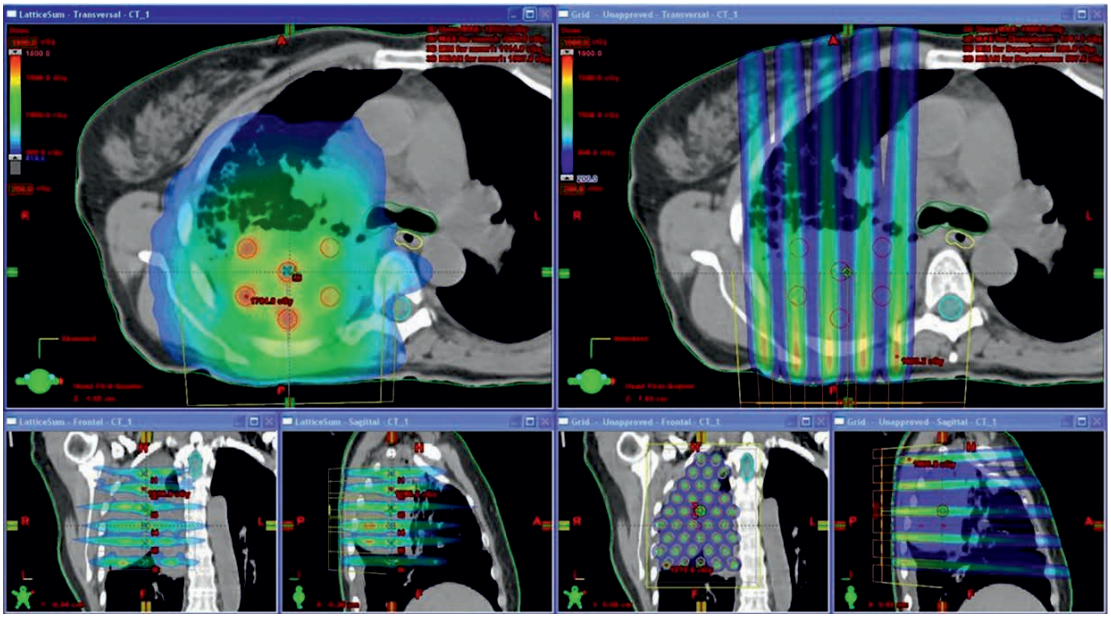

Figure 7- 2D Grid vs 3D LATTICE in SFRT (Courtesy-Spatially fractionated RT: History, present and future)

Despite advancements in the field of oncology, the clinical outcome in patients with bulky tumors has been poor. A recent study using the SFRT concept called SBRT-PATHY; targets high doses of radiation stereotactically to partial tumor only, wherein only the hypoxic fragment of the bulky and unresectable tumor receives high doses of radiation to counter radioresistance resulting in bystander effects locally and abscopal effects at distant sites. This concept was investigated in a clinical study in which high doses of radiation were delivered to a partial fragment of the unresectable tumor to counter hypoxia resulting in an average reduction of 70% in the size of the tumor, demonstrating its potential role in the neo-adjuvant setting to facilitate resectability of the tumor.[25]

In the modern era of particle therapy, protons are being increasingly used to deliver SFRT. Since protons have the specific benefit of lowering or eliminating the exit dose in normal tissues beyond or distal to the tumor due to its characteristic physical property of the "Bragg peak" and less scattering in normal tissues, Using SFRT/ GRID with protons, the depth dose curves rapidly decrease beyond the target, resulting in a more consistent beamlet dose within the tumor. Various studies have shown that contemporary proton beams used in the clinics, while treating deep-seated tumors, have the ability to not only reduce the radiation exposure to organs at risk (OARs) distal to the target(tumor) but also decrease the radiation dose to the OAR's proximal to the target.[26]

Superior technologies for delivering SFRT are presently being developed to improve radiation delivery.[27,28] Minibeam (MBRT) is one such technology that has a beamwidth of 500–700 microns which is wider than MRT (beam width 25 to 100 micrometers.[28]

The benefits of SFRT include improved firepower (high BED), less toxicity, and increased precision.[29] Although, in its nascent stage, with its current application being limited to palliative therapy and in recurrent tumors. However, with the ever-evolving advancements in

technology and a better understanding of its radiobiology, SFRT has the potential to be incorporated as a definitive treatment option following rigorous clinical trials.

MRI AND PETCECTBASED RADIOTHERAPY SYSTEM:

Over the past few years, magnetic resonance imaging (MRI) guided linear accelerators (LINAC) devices have gained popularity. The Elekta Unity and the Viewray MRIDIAN systems are the two systems that are now available in the US markets.[30,31]Real-time imaging during radiation delivery makes image-guided radiotherapy systems superior to traditional LINACs. The system includes a dynamic MRI to monitor patient movement, tumor movement, and normal tissue movement. Although these technologies provide the ability for safer and more accurate therapy administration, the treatment sessions are substantially longer.

Another image-guided system that is getting attention is the Reflexion X1 LINAC system.[32]It has recently got US FDA approval for standard IMRT, SBRT, and SRS. It is designed for biologically guided radiotherapy. This device can image metastases and has PET radiotracer detectors. The system can target each patient with real-time adaptive radiotherapy.

Figure 8- View ray MRIdian system (Source: Henry Ford Health, 2022: Online)

Figure 9- Reflexion X1 LINAC system (Source: Reflexion Medical, 2022: Online)

Artificial Intelligence (AI) In Radiotherapy processes:

Artificial intelligence (AI) is the ability of a machine to mimic human intelligence. Artificial intelligence (AI) algorithms are being exploited in the field of radiation oncology at various levels. Contemporary radiation therapy workflow can be classified into several essential processes such as diagnostic imaging, simulation, treatment planning (TP), quality assurance, radiation delivery, radiotherapy verification, and patient monitoring.[33]Artificial Intelligence is being utilized at each and every step of the radiotherapy workflow allowing seamless integration of each process.

AI and machine learning algorithms are being enthusiastically explored in present-day clinical imaging methods, such as computed tomography (CT), magnetic resonance imaging (MRI), or Positron Emission Tomography (PET) that assist in not only radiation planning but also in treatment execution.[34] AI-based algorithms offer non-radiative solutions and have been extensively researched in recent years. The AI-based algorithm is being primarily implemented in three aspects of medical imaging: Image segmentation, medical image registration, and Computer-aided detection (CAD) and diagnosis system.[35]

In radiotherapy treatment planning processes, various computer optimization algorithms are being exploited. Inverse planning simulated annealing (ISPA) and hybrid inverse planning optimization (HIOP) are two examples of the algorithms employed.[36] Convoluted Neural Network (CNN)-based automated systems have been used in planning patients of prostate cancer patients treated with IMRT technique and have been demonstrated to be extremely precise in classifying treatment plans meeting the required planning goals vis-a-vis plans not meeting the planning goals.[37]

Although AI has limitless promise for radiation processes, it is not yet sufficiently mature for widespread usage in clinical settings. Although statistically speaking artificial intelligence (AI) appears excellent, it is far from ideal because of its inaccuracy in some treatment procedures and its propensity to make errors that a human would not. Before being used in clinical settings, the algorithm must also undergo comprehensive accuracy testing, which is often time-consuming and expensive. However, AI has significant promise for improving radiation therapy planning and delivery in the future.

Conclusion:

Radiation Therapy planning and the technology in delivering radiotherapy to cancer patients have undergone a paradigm shift over the last decade, with the advent of fast and sophisticated computing technology and the hardware to deliver highly conformal radiotherapy to the tumor with the sparing of the surrounding normal tissue. This has revolutionized its clinical use in the contemporary era; however, radiation therapy is an interface between radiation physics, radiation chemistry, radiobiology, and medicine. Utilizing all of these factors will enable us to personalize radiation therapy by improving target delineation, avoiding normal tissue, dose escalation, dose fractionation, and treatment response prediction.

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