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RADIATION THERAPY AN OVERVIEW: A JOURNEY OF TECHNICAL ADVANCEMENTS

Oncology

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ABSTRACT

Radiation is used for diagnostic and therapeutic purpose both. Radiation Therapy is being used as primary definitive treatment or as adjuvant treatment for various malignancies. In Radiation Therapy we use the ionizing radiation to kill the tumour cells along with minimal damage to surrounding normal tissue. With the advancement in imaging and treatment modalities and techniques, now we can escalate the radiation dose to the tumour along with better sparing of surrounding normal tissue. In this article we are trying to review the various important aspects of radiation like its evolution and new advancements in radiation techniques.

KEYWORDS

Image Guided Brachytherapy, Stereotactic Body Radiotherapy, Surface Guided Radiotherapy, 4π radiotherapy.

Introduction:

Since the inception of Radiation Therapy soon after the discovery of X-rays by Roentgen in 1895, various advances have been made in Radiation Therapy machines, techniques, planning and delivery process. During the first 50 years of Radiation Therapy the technological progress was relatively slow and mainly based on X ray tubes, van de Graaffe generators and betatrons. The invention of the *^{60}Co teletherapy* unit by H.E. Johns in Canada in the early 1950s[1] provided a tremendous boost in the quest for higher photon energies and placed the cobalt unit at the forefront of Radiation therapy for a number of years. With the time*, medical LINAC* became the most widely used radiation source in modern Radiation therapy. With its compact and efficient design, the linac offers excellent versatility for use in Radiation therapy through isocentric mounting and provides both either electron or megavoltage X ray therapy with a wide range of energies. With the time Various advancements made in radiation techniques, planning and delivery also, *like 3D CRT, IMRT, IGRT, VMAT, Proton therapy, Carbon ion therapy, Neutron beam therapy, IORT, SRS/SRT*, *refinement in fractionation* [2](Chou et.al) and *image guided brachytherapy* etc.

Principle:

The main goal of radiation therapy is to shrink the tumors by killing cancer cells with minimal damage to normal cells. The biological target of radiation in the cell is DNA[3]**.** By direct or indirect effects, it leads to Double stranded DNA break and cross linking[4] and ultimately destruction of cells. Rapidly proliferating cells are more radiosensitive than normal cells. Normal cells have the better ability to repair than tumour cells, leads to differential tumour cell killing [5]. So our aim is to optimize the dose to tumour cells with minimal damage to surrounding normal cells, called *Therapeutic ratio* (Neal and Hoskin 1997)[6].

Mode of Techniques

- Teletherapy
- Brachytherapy
- Radioactive isotopes

Teletherapy

In it, source of radiation is kept at a distance away from the patient. Depending on the energy, it is mainly categories into two types-

- Kilovoltage therapy[7]
- Superficial X-Ray (50-150 kV)
- Orthovoltage X- rays (150-300 kV)
- Megavoltage therapy
- Co^{60} gamma rays (1.17-1.33 Mv)
- Linear accelerator (4-25 Mv)

Megavoltage radiation has various advantages over kilovoltage radiation most important is skin sparing effect. In 1932 megavoltage radiation era was started with the development of van de Graaffe generator. With the time in 1950s, Co^{60} machine was introduced. Installation of the first clinical linear accelerator began in June 1952 in the Medical Research Council (MRC) Radiotherapeutic Research Unit at the Hammersmith Hospital, London[8]. In 1960s design developments led to the appearance of higher megavoltage energy machines, as well as the first dual modality accelerator. During 1970s to 1990s, multiple energy accelerators with smaller mechanical tolerances and larger maximum field sizes, as well as the concepts of conformal therapy, automatic and dynamic wedges, electronic portal imaging devices and computer-controlled verification systems were introduced.

In present era, LINAC have replaced Co^{60} for the following reasons-

- Capable to produce variable dose rates
- Increased skin sparing effect
- Narrower penumbra
- Multimodalities available in same machine(electron & Photon both)

Network capabilities between accelerator and the treatment planning computer, simulator, CT/MRI suites, other treatment machines and the automated patient booking system.

Brachytherapy

The term brachytherapy was first proposed by Dr G Forsell in 1931[5]. The NCRP (1972) defined the term brachytherapy as a method of radiation therapy in which an encapsulated source or a group of such sources is utilized to deliver gamma or beta radiation at a distance of up to a few centimetres, either by surface, intracavitary or interstitial application[9]. Sources suitable for brachytherapy use consist of small amounts of radionuclide which are totally encapsulated by a nontoxic and inert material, such as stainless steel or platinum. The radioactive sources come in the form of small needles, wires, rods or spheres. The commonly used radioisotopes are $Radium^{226}$, $Cesium^{137}$, $Iridium^{192}$ and $Iodine^{125}$.

Techniques[9]-

Preload- Earlier the radiation source was directly handled by the staff, which causes significant exposure to radiotherapist and other staff.

Afterload- It was first started in 1960s. It is of two types-

- Manual after loading- In this technique we first insert the metal/plastic hollow tube inside the tumour and after verifying the position with radiograph, sealed radioactive source is inserted manually.

Remote after loading- It is same as manual after loading except that source is mechanically driven in and out automatically.

Brachytherapy may be administered using HDR (1200 or more cGy/hr.), MDR (200-1200 cGy/hr.) and LDR (40-200 cGy/hr). In this era, we are using HDR after-loading brachytherapy. It has single active source, commonly Ir^{192}, which moves in steps to a programmed positions. It is mechanically driven in and out of the applicator. Recent advancements in brachytherapy are *Image guided Brachytherapy* (In it we use the image guidance (MRI, U/S) for optimization of dose), *Electronic brachytherapy* and *stereotactic brachytherapy.*

Radioactive Isotopes-
These are either injected or taken orally to treat tumour. Commonly used isotopes are I^{131}, P^{32}, Y^{90}, Sr^{89}, Sm^{153}, Lu^{177}, and Ra^{223}.

Fractionation in Radiation Therapy-
Initially radiation was used as single large exposure which causes extensive normal tissue toxicity with lesser tumour control[10]. Fractionated radiation has many advantages-

Dividing a dose into several fractions spares normal tissues by
- Repair of sub lethal damage between dose fractions
- Repopulation of cells

  Dividing a dose into several fractions increases damage to the tumor by
- Reoxygenation of tumor environment
- Reassortment of cells into radiosensitive phases of the cell cycle between dose fraction

Prolongation of treatment reduces early reactions.

However, excessive prolongation allows surviving tumor cells to proliferate.

There are various refinements in fractionation schedule for increased therapeutic ratio. Which are as follows-

- Hyperfractionation- In this two or more fractions of radiation are given per day with at least 6 hr. interval in between[11]. By this we can increase the total dose with overall treatment time same as conventional fractionation. There is no increase in late reactions.
- Accelerated fractionation- In it treatment time shortened with same total dose. We give two or three fraction per day. It is to reduce the repopulation of tumour cells (regeneration)
- Concomitant boost technique- In it treatment is delivered once daily for the first 3.5 weeks and then twice daily during the final 2 to 2.5 weeks, when tumor cells can begin to repopulate more rapidly[5].
- Accelerated hyperfractionation- It has the features of both Accelerated fractionation and hyperfractionation.

Advancement in Radiation Machines & techniques-
Imaging modalities- The determination of the target volume that is related to the extent of the disease and its position relative to adjacent critical normal tissues can be achieved with various methods. These range from a simple clinical examination through planar X ray imaging to the use of complex modern imaging equipment such as EPID, MSCT, USG, MRI, SPECT and FDG-PET scanners[12].

Cyber Knife- Cyber Knife consists of a compact X-band 6 MV linear accelerator coupled to a multi-jointed robotic manipulator with 6 degrees of freedom[13]. The current generation of Cyber Knife technology consists of two precisely calibrated diagnostic x-ray tubes fixed to the ceiling of the treatment vault and two nearly orthogonal aSi flat-panel detectors. After coarse alignment, projected images from the cameras are automatically registered with the DRRs from the planning CT. Changes in target position are relayed to the robotic arm, which adjusts pointing of the treatment beam. During treatment, the robotic arm moves through a sequence of positions (nodes). At each node, a pair of images is obtained, the patient position is determined, and adjustments are made.

Tomotherapy- The Tomotherapy technique was developed in the early 1990s at the University of Wisconsin–Madison by Professor Thomas Rockwell Mackie and Paul Reckwerdt[14]. In Tomotherapy or helical Tomotherapy the radiation is delivered slice-by-slice. HT is a form of CT guided IMRT. In HT a narrow intensity modulated pencil beam is delivered from a rotating gantry while the patient is simultaneously moved through the bore, compared to the much wider intensity modulated beam and static patient in conventional IMRT[15]. HT units are therefore better able to target treatment sites throughout the body without a pause. It is generally used in H&N, GI, CNS, Gynaecological and Genito urinary malignancies.

Flattening Filter Free Accelerator[16] (True Beam) - In conventional linear accelerators, uniform intensity across the treatment field is obtained by placement of a flattening filter in the beam. However, modern radiotherapy practice now routinely utilizes fluence modifying techniques, such as intensity-modulated radiation therapy (IMRT), to create more conformal dose distributions. In such cases, the flattening filter becomes unnecessary in the beam production process. Additionally, for small fields, even without the flattening filter the treatment field is nearly flat over the central few centimetres. The primary purpose of the FFF X-rays is to provide much higher dose rates (2400 MUs /Minute) available for treatments[6]. FFF is an advanced image-guided radiation therapy (IGRT) system used to treat cancer with speed and accuracy. FFF combines respiratory gating, real-time tracking, imaging and treatment in a streamlined system. With this integration, we can do stereotactic radiosurgery (SRS), stereotactic body radiation therapy (SBRT), image-guided Radiation Therapy (IGRT), intensity-modulated Radiation Therapy (IMRT), Calypso beacon tracking, Rapid Arc and Gated Rapid Arc.

Radiation Techniques-
Initially we were using Two-dimensional (2D) Radiation Therapy which consist of a single beam from one to four directions. Beam set ups were usually quite simple consisting of opposed lateral fields or four field "boxes" but because of close proximity to critical organs like spinal cord, eyes, optic chiasma, etc., quite often delivery of maximal dose to tumor was not feasible. With advancements in computer and imaging technology, now we can deliver higher dose to the tumor with better sparing of critical organs.[12] Advances in our ability to shape and modify intensity of radiation beams have also led to major treatment planning advances. Beam shaping was initially accomplished by custom designed metal blocks (or wedge) mounted in the head of the treatment machines or tissue compensators. Over the past decade, this technique has been replaced by multileaf collimators (MLCs), which consist of small metallic leaves (40 to 120 pairs of tungsten leaves), located in the head of linear accelerator. Each leaf within MLC is robotically controlled and moves independently of the others to create computer-controlled beam shapes.

3D-CRT- *3D-Conformal radiotherapy* based on 3D anatomic information in which dose distribution conforms to the target volume closely in terms of adequate dose to tumor & minimum dose to surrounding normal tissues. In it we use CT scans to localize tumor in 3-D for more precise treatment planning. The 3D CRT plans generally use increased number of radiation beam (3-6 beam angles), conventional beam modifiers (e.g., wedges and/or compensating filters) and MLCs, to improve the dose conformality.

IMRT- *Intensity Modulated Radiation Therapy* refers to a conformal radiation therapy technique in which non-uniform fluence is delivered to the patient from any given position of the treatment beam using computer-aided optimization to attain certain specified dosimetric and clinical objectives. It is more conformal than 3D CRT with a sharp dose fall off at PTV boundary which reduces the normal tissue dose. Large fields and boost fields can be integrated in single treatment plan (SIB) which offer an additional radiobiological advantage.[17]

IGRT- In *Image guided Radiation therapy* we do the positional verification using imaging (CBCT, Portal imaging) prior to each treatment fraction. This helps to improve the precision and accuracy of treatment delivery. IGRT is used to treat tumors in areas of the body that move, such as the prostate, lungs etc. In lung we do 4 dimensional IGRT (Gated IGRT).

VMAT- *Volumetric modulated arc therapy* is a novel radiation technique and advancement of IMRT, which can achieve highly conformal dose distributions with improved target volume coverage and better sparing of normal tissues. The machine continuously reshapes and changes the intensity of the radiation beam as it moves around the body. VMAT also has the potential to offer additional advantages, such as reduced treatment delivery time compared with other techniques.

Stereotactic body Radiation Therapy & Stereotactic radiosurgery- Stereotactic irradiation comprises focal irradiation techniques that use multiple, non-coplanar radiation beams and deliver a prescribed dose to pre-selected and stereotactically localized lesions. In SRS we generally deliver total dose in single fraction and primarily in brain lesions. But in SBRT, we use multiple fractions for the same and primarily in tumours other than CNS. SRS & SBRT can be delivered with cyber knife, Tomotherapy, Proton etc. Now we can do the *stereotactic brachytherapy* also in which we can do temporary or permanent implant into the tumour.

Intraoperative Radiation Therapy- In it a single large radiation dose is delivered directly to the tumor bed in the operation theatre after defining the tumor area and nearby normal organs. In IORT we are wiser to define the target volume and to spare normal structures. In IORT we give 12- 20 Gy in single fraction. IORT can be delivered with electron *(IOERT),* high dose rate brachytherapy with Ir^{192} *(HDR-IORT)* and low kV x-rays *(KV-IORT)*.

Neutron beam therapy- When an accelerated proton or Deuteron interacts with target (Be) it produces Neutron beam. Neutron beam is used to treat hypoxic cancer cells and tumours which are relatively radiation resistant. Neutron is high LET radiation so it produces denser ionization and cause greater injury to kill hypoxic cancer cells and radiation resistant tumours. It is generally used in unresectable, residual or recurrent salivary gland tumor.[18]

Charged Particle therapy- Photon and electron beams are the primary techniques for radiation. But now new particle like Proton and heavy ions like helium or neon have been developed for treatment of cancers. Recently, a heavy charged particle like carbon is having clinical interest. It is like Proton but have higher relative biological effectiveness (RBE) than proton. Charged particle therapy does not gain much popularity because there are only limited number of indications (eg. Unresectable skull base and cervical spine tumours).

Electron beam therapy- Electron beam radiation is a special type of Radiation Therapy that consists of very tiny electrically charged particles generated in a machine called a linear accelerator and directed towards the skin. Electron-beam therapy is advantageous because it delivers a reasonably uniform dose from the surface to a specific depth, after which dose falls off rapidly, eventually to a near-zero value. Electron beams with energies up to 20 MeV allows disease within approximately 6 cm of the surface to be treated effectively with sparing deeper normal tissues. Electron therapy is used to treat the cancers of skin, Head & Neck[19], Chest, Upper respiratory and digestive tract. *TSET* is a special technique to treat whole skin like in *Mycosis fungoides*.[20]

Proton Therapy[21]- Proton is the most commonly used charged particle for treating cancer. It is produced by cyclotron and Synchrotron. Due to its unique energy absorption profile in tissues, proton beam therapy is one of the highly conformal radiation techniques. Protons have a finite range like electrons but at the end of their range, occurs the Bragg peak, where they deliver maximum dose. By appropriately adjusting the energy of proton beam, we can position the Bragg peak within tumor almost anywhere in body, sparing normal tissues both proximal and distal to tumor. This is especially important in children, as they are more sensitive to radiation-induced cancer than adults. Protons have virtually no side scatters, which add to therapeutic ratio.

Carbon ion therapy- Carbon ion therapy is an innovative radiation technique, that is mostly dedicated to cancers which are unresectable and radioresistant to photons. It has properties like protons ie. highly conformal, finite range in tissue with Bragg peak but it has higher relative biological effectiveness and narrow penumbra than protons.[22]

Adaptive Radiation Therapy- A single plan, designed before treatment, is insufficient to describe the actual dose delivered to tumour and often leads to suboptimal treatment that's why adaptation is needed. The term "*Adaptive Radiation Therapy*" was introduced by Yan et al. (1997).[23]

"*Adaptive Radiation Therapy*" is defined as changing the radiation treatment plan delivered to a patient during a course of Radiation Therapy to account for temporal changes in anatomy (e.g. Tumor shrinkage, weight loss or internal motion) & changes in tumor biology/function (e.g. Hypoxia). ART is generally used in Prostate, Head and Neck, Lung, Cervix and Bladder cancers.

Radio immunotherapy[24]- In radio immunotherapy, radioisotopes are attached to the tumor-specific monoclonal antibodies, which are injected into the body and they actively seek out the cancer cells and destroy them by the cytotoxic action of radiation. Radio immunotherapy is most commonly used in the treatment of blood cancers, such as leukaemia and lymphoma.

4 π Radiotherapy - 4π radiotherapy is a non-coplanar IMRT technique that has demonstrated superior OAR dose sparing compared to VMAT in various tumor sites, including the prostate. 4π radiotherapy incorporates non-coplanar beams distributed on the 4π spherical surface. 4π optimization begins with a candidate pool of 1162 non-coplanar beams, each 6° apart in the 4π solid angle space. Using a computer assisted design (CAD) model of the Varian TrueBeam machine and a 3D human surface model, each angle is simulated and subsequently eliminated if a collision is predicted between the gantry and the couch or patient. Inverse optimization is performed by using a *greedy column generation algorithm* to iteratively select 30 non-coplanar beams with integrated fluence map optimization.[25]

Surface Guided Radiation Therapy - Surface Guided Radiation Therapy (SGRT) is a rapidly growing technique which uses stereo vision technology to track patient's surface in 3D, for both setup and motion management during radiotherapy. SGRT can be used to ensure accurate patient positioning during treatment without an additional delivery of dose to the patient[26]. The overall results are within good agreement. SGRT also enables contactless, non-invasive reconstruction of 4D CT data. SGRT can be used in the treatment of breast, brain, head and neck cancer, sarcoma, and other conditions.

Hyperthermia and Radiation – In Hyperthermia we achieve tumor temperature in the range of 40°C to 45°C and to maintain that for a time period of 1 hour. Hypoxic cells and cells in S- phase of cell cycle are radioresistant but when heated, they become radiosensitive. Hyperthermia causes reoxygenation which will improve the radiation response. Hyperthermia inhibits the repair of sublethal and potentially lethal damage by inactivating the crucial DNA repair pathways.[27]
By these above mentioned mechanism, Hyperthermia can act as radio-sensitizer. It also shows synergism with some chemotherapeutic agents.

Conclusion-
In the past few decades, there are immense advancements in radiation techniques and imaging modalities. Imaging and computer science is increasing the capability but also the complexity of Radiation Therapy. Now we can escalate the tumor dose with better sparing of normal tissues which leads to better tumor control. Now we are going towards *Tumor Biology Guided Radiation Therapy (BGRT)* which will be more tumor and patient specific. But these new techniques require expertise and large financial support for their setup and implementation. Although these new techniques are great but a little difficult to set up and implementation so not readily available.

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