NEW PARADIGMS IN RADIATION ONCOLOGY WITH MODULATION OF EVOLUTIONS IN MEDICAL PHYSICS

Authors

Dr. Anoop Kumar Srivastava
Ph. D
Additional Professor
Department of Radiation Oncology
Dr Ram Manohar Lohia Institute of Medical Sciences
Lucknow, India

Dr. Avinav Bharati
Ph. D
Associate Professor
Department of Radiation Oncology
Dr Ram Manohar Lohia Institute of Medical Sciences
Lucknow, India

Dr. Madhup Rastogi
M D, Professor & Head
Department of Radiation Oncology
Dr Ram Manohar Lohia Institute of Medical Sciences
Lucknow, India

Dr. Shiv Shanker Tripathi
M D, Additional Professor
Department of Emergency Medicine
Dr Ram Manohar Lohia Institute of Medical Sciences
Lucknow, India

Dr. Swagat Mahapatra
Associate Professor
Department of orthopaedics
Dr Ram Manohar Lohia Institute of Medical
Sciences, Lucknow, India

Dr. Deepti Srivastava
Assistant Professor
Department of Horticulture
CBGAg PG College ,BKT
Lucknow, India

"Life is a state of constant radiation and absorption; to exist is to radiate; to exist is to be the recipient of radiations"

William George Jordan

I. AN OVERVIEW

The Nobel Prize winning discoveries the X ray by Roentgen in 1895 and radioactivity by H. Becquerel in 1896 initiated the use of physics in medicine and first therapeutic use of X ray was to treat a patient of breast cancer on January 29, 1896 by E.H. Grubb and company with low voltage X-Ray unit. Without understanding the physics behind X-rays and radioactivity it would have been lethal to apply on humans. Since then, it has emerged as specialized branch in allied health science for three vital areas of medical sciences

- Radiation Oncology
- Radiodiagnosis
- Nuclear Medicine

Radiation treatment to a cancer patient is a multistep procedure. Every step is equally important and surprisingly physics is deeply involved at every step be it imaging, dose measurements, treatment planning or treatment delivery. To understand the current status of medical physics in radiation oncology, it is necessary to comprehend the evolution of radiation oncology technology in conjunction with medical physics.

Table 1: Physics milestone advancements in radiation therapy.

***(**Curtesy: T Bortfeld and R Jeraj ,The British Journal of Radiology, 84 (2011), 485–498)

Fundamental discoveries leading to new treatment and imaging modalities

1895: Discovery of X -rays (Nobel Prize in physics for Ro ̈ntgen in 1901) leading to X-ray (CT) imaging and first radiation treatment of cancer with X-rays only 1 year later

1896: Discovery of radioactivity (Nobel Prize in physics for Becquerel/Curie in 1903) leading to the first treatment with radioactive isotopes shortly thereafter 1919: Discovery of the proton, leading to the first patient treatments with a proton beam in 1954

1938, 1946: Discovery of nuclear magnetic resonance (Nobel Prize in physics for Rabi in 1944 and Bloch and Purcell in 1952), leading to MRI in the 1970s

Technology inventions in radiation dose delivery

1951: Cobalt-60 treatment machines become clinically available: use of high-energy gamma rays for better skin sparing

1953: Linear accelerators with higher energies for better skin sparing and improved penumbra 1950s Cyclotrons for proton therapy (physics Nobel Prize for Lawrence in 1939)

1986: Radiation field shaping with multi-leaf collimators

1994: Intensity modulated radiation therapy (IMRT)

Technology inventions in treatment planning

1960s Use of computers for dose computation

1980s Development of three-dimensional treatment planning

1987 Inverse treatment planning and plan optimisation techniques

Technology inventions in imaging

1972 CT (Nobel Prize in Medicine for Cormack and Hounsfield in 1979), which is soon used for radiation treatment planning

1970s MRI (Nobel Prize in Medicine for Lauterbur and Mansfield in 2003)
2000s Imaging integrated into treatment machines for image guided radiation therapy

Medical Physics and Modern Radiotherapy

Radiotherapy has utilized medical physics in its maximum capacity in terms of Dosimetry, CT simulator, Treatment planning systems and Treatment units

II. DOSIMETRY

The process to quantify the radiation is a critical step of accurate dose delivery to patient. Proposal of Röntgen based dosimetry was initiated in 1902 by Guido Holzknecht of Austria. In 1928 at first conference of Association of International Radiology in Sweden use of ionization chamber was adopted for radiation dose measurements. Since then, the advancement in the dosimetry instruments and techniques have changed a lot. Conversion of radiation dose to quantifiable unit was a big issue till calibration factor in terms of dose to water were in practice so that doses could be measured directly in Gy, the SI unit of dose. From free air ion chamber technology to current era of diamond detectors, the accuracy of dose measurements has achieved a least count of µGy level with and spatial resolution of submillimeter level. It has impact on design of miniaturized detector assembly for various dosimetry procedures. The advancement in detector technology has put the whole chain of radiotherapy at a different level. Now we are in position to have a better image resolution in simulation which leads to better treatment dose calculation, better treatment position verification and hence a better treatment.

III. TREATMENT SIMULATION

In 1967 G Hounsfield invented the first CT scanner and shared Nobel prize in medicine in 1979 with Cormack, basically a physicist. CT scanner was soon put to use in clinical practice and it has evolved generations after generations. In 1971 time taken to acquire one image was nearly 5 minutes, which has reduced to few milli seconds in present days. The current technology of photon counting detectors provides CT data at a very high spatial resolution and that with. Better signal to noise ratio at lower dose. Accurate dose calculation in treatment planning requires actual attenuation coefficient for different components of human body viz tissue, bone etc. This was the basic reason to invent CT scanners because it was then related to differential absorption of radiation by human body. This became pathbreaking discovery as most of the treatment planning systems uses algorithms which uses the change in electron density as basis of dose calculation and CT numbers can directly be converted to electron density. The earliest commercial CT simulator was available in 1994 by AcqSim Oncodiagnostic Simulation/Localization System, Marconi Medical Systems, Inc. Modern day CT simulators are equipped with flat table-top of carbon fiber for least attenuation and other accessories like moving lasers, and seemless connectivity via DICOM network etc.

Figure 1: earliest commercial CT simulator was available in 1994 by AcqSim Oncodiagnostic Simulation/Localization System, Marconi Medical Systems, Inc.

IV. TREATMENT PLANNING SYSTEMS (TPS)

Treatment planning is a vital procedure in the chain of radiotherapy delivery. Treatment planning system is a computer with specific hardware and software for radiation treatment planning. Treatment planning includes delineation of target and Organ at risk for further beam placement to attain a clinically acceptable result in terms of target coverage and tissue tolerance. In early nineties the dose delivery was based on manual calculation based on isodose charts. Three-dimensional dose calculation, its visual display on CT sections and dose optimization came into play only after availability of powerful computers in 1960s with high RAM/ROM capacity to handle and compute complex data of the patient. The cost-effective computers made the task easier when medical physicists started developing calculation and treatment plan evaluation algorithms such as pencil beam, convolution, collapse cone, superposition and mote Carlo. The idea of inverse optimization changed the whole scenario of treatment planning from treatment plan to dose distribution-based evaluation to dose constrained based treatment planning i.e., IMRT. and now a days is totally computerized based on various calculation algorithms provide more degree of freedoms for treatment planning. The development in medical physics has made this part the hub of unbroken chain of radiotherapy. Figure 1 depicts the 100 years of development in radiation oncology from 1900 to 2000.

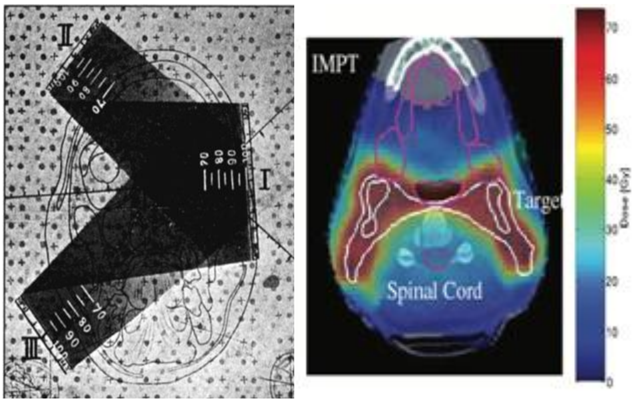


Figure 1: 100 years of development in radiation therapy have made a difference. Comparison of an X-ray treatment plan from the early 1900s (a) and a proton treatment plan from the early 2000s ((b), courtesy of AW Chan and AV Trofimov, MGH Boston).

Courtesy: T Bortfeld and R Jeraj, The British Journal of Radiology, 84 (2011), 485–498

V. TREATMENT DELIVERY

The treatment delivery techniques have evolved from kV therapy, Orthovoltage therapy (Early Nineties) to Cobalt-60 teletherapy unit (1951) and finally to the stage of high-end Linear accelerators (1953) and Proton therapy etc.

All these developments are due to synergistic effort in the field of Medical Physics, electronics and microwave technology etc.

Radiotherapy treatment delivery is broadly divided in two categories

1. **External Beam Radiotherapy and 2. Brachytherapy**

2. **External Beam Radiotherapy:** It is the technique of radiotherapy where the radiation source is at a certain distance from the patient and is divided on the basis of planning techniques such as

   - **3D conformal radiotherapy (3DCRT):** It uses standard radiation beams in conformity with target to achieve a desired dose distribution while attempt to spare the normal structures as much as possible.

   - **Intensity Modulated Radiation Therapy (IMRT):** It is advanced form of 3DCRT and uses the principal of inverse treatment planning. It is constraint-based treatment planning in which constraints for target as well as normal structures and plans are optimized and generated to attain result close to desired constraints.

   - **Volumetric Modulated Arc Therapy (VMAT):** It is one step ahead to IMRT which has more degrees of freedom such as dose rate variation, Gantry speed variation etc. during treatment.

- **Stereotactic radiosurgery (SRS):** Stereotactic radiosurgery and Stereotactic radiotherapy have a vital role to play specially in small tumors may be single or multiple of brain.

- **Stereotactic body radiotherapy (SBRT):** Stereotactic body radiotherapy has shown roe in treatment of lung lesions.

Linear Accelerators capable of delivering Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) revolutionized the whole treatment delivery technique in radiotherapy when IMRT was first executed in 1994. But challenges were there as it involves most of the time dose escalation to the targets in comparison to Conventional and 3DCRT. IMRT/VMAT involves a special type of imaging, treatment planning, treatment verification and delivery procedure. During Imaging special type of immobilization is required to minimize the perturbation at the interface of skin and immobilization cast. Further as we can do dose escalation without taxing much on normal tissues.

3. **Brachytherapy:** Brachytherapy is a type of treatment where radiation source is placed in close vicinity of the target. First conformal treatment is considered to be brachytherapy. Brachy is a Greek word which means close distance. Modern day Brachytherapy utilizes shield sources and have evolved from unshielded implants to today's era in various forms.

- **Intracavitary Brachytherapy:** It is one of the important supplementary treatment for cancer cervix along with external beam radiotherapy. With the advancement in medical physics, it has shifted from manual after loader to remote after loaders with miniature sources like Co-60 and Ir-192. Also, the treatment planning techniques changed from X ray based to CT/ MR based. Now we are able to plan directly on MR images as per various international guidelines due to availability of non-ferrous applicators.

- **Interstitial Brachytherapy:** This technique of brachytherapy allows to place the thin catheters to treat the superficial/ deep seated tumors of breast, head and neck etc.

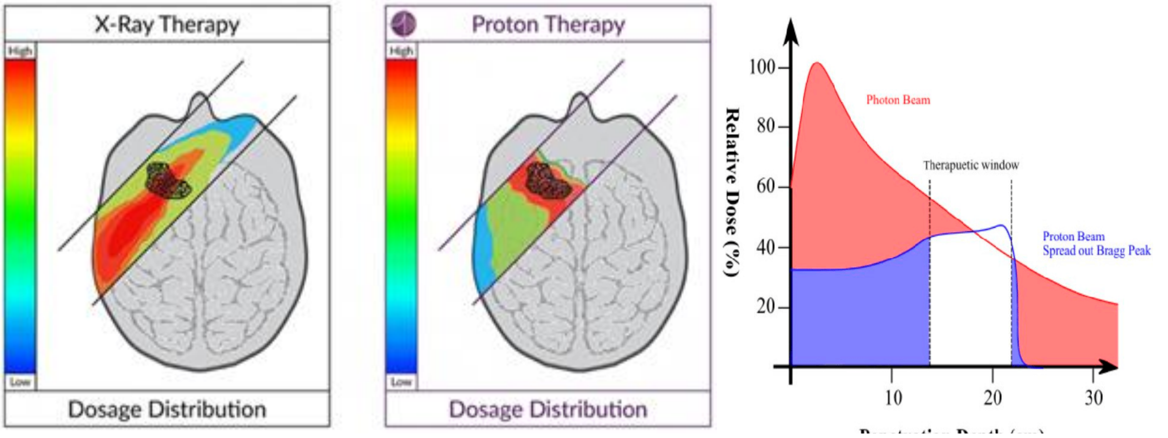
- **Intraocular Brachytherapy:** Used for treatment of eye in which a thin gold sheet with radioactive seeds is used.

- **Intraluminal Brachytherapy:** Used for treatment of lumen like esophagus, lung and gall bladder etc.

- **Electronic Brachytherapy:** This has created an all together a different scenario in brachytherapy as it uses miniature X ray sources instead of radioactive sources. The main advantage of electronic brachytherapy is regarding radiation safety as there is no radiation when it is in off condition.

Future: Although everything practiced today is considered to be modern but some have been a game changer due to medical physics. Few of them are described here as future of radiotherapy.

- **Proton therapy or heavy ion therapy:** Proton therapy basically explores its mass and charge property. The physical dose distribution is directly dependent on energy and hence on range and finally the Bragg peak. Bragg peak defines the range of proton.



Change in beam scanning techniques from passive scattering (where compensators and metal apertures were in use) to pencil beam scanning has resulted in better dose distribution with minimal neutron contribution but the uncertainty in range prediction is a limiting factor however with the help of on-board tracking of Carbon 11 and Oxygen 15 isotopes which are produced in human tissue just before proton beam stops with the help of Functional imaging like positron emission tomography (PET).

- **FLASH radiotherapy:** Normal tissue complication has always been a challenge for radiotherapy. Flash radiotherapy is however still in investigational phase but it has a promising role as far as treatment time and normal tissue damage caused due to radiation is concerned. It has a capability to treat a patient in few seconds with a single ultra-high dose-rate of nearly 40 Gy/second. The very first use of FLASH RT on human was in 2018.FLASH RT may have a widely accepted future if we could use X-ray instead of protons as it would be cost effective also.

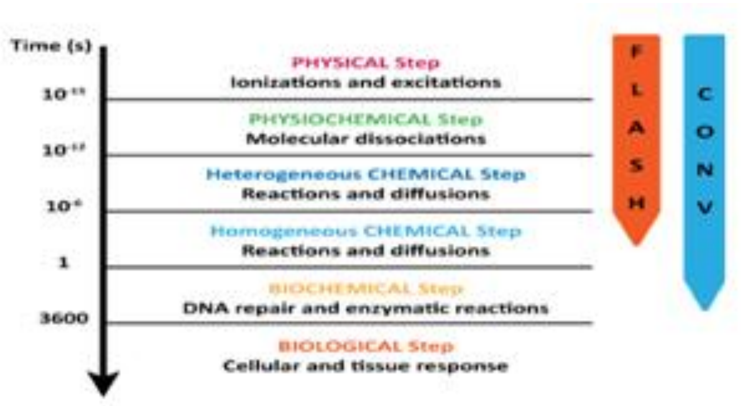


Figure 3: comparative timeline of Flash RT and Conventional RT
Courtesy:Vozenin, Spitz, Limoli

Its radiobiology and clinical acceptability have to be established before it is commissioned for patient treatment through phase III trials.

- **Radiobiological treatment planning and evaluation:** At present Only Few commercially available treatment planning systems are partially using radiobiological parameters in treatment planning but evaluation is still based on physical parameters. There is a potential to use radiobiology for final evaluation and clinical judgments based on it. Few radiobiological tools based on various platforms like MATLAB (DREES etc.) and Python. Fewer are available for windows also and they don’t require much of training in programing language. All these can be used effectively if brought in practice but this only needs human resource as they are not part of treatment planning and evaluation software. Its integration with treatment planning software may change the whole scenario of treatment plan evaluation and will create a real time correlation between a biological action of radiation and its outcome.

- **Effective motion management:** Motion Management has been an integral challenge since the inception of radiotherapy. With the inclusion of time, the fourth dimension in addition to three space coordinates has shifted the paradigm of radiotherapy to another level. Both internal and external motions now can be corrected with the help of motion-correlated imaging that reduces the motion blurring effect and effectively freezes motion, deformable image registration between different snapshots in time to track the position of each voxel in the patient as a function of time, fast-dose calculation and dose (re-)optimization for dynamic dose accumulation, and the ability to deliver radiation in sync with patient motion (in the case of respiratory and other fast-breathing motion).With the inclusion of time, the fourth dimension in addition to three space coordinates in treatment planning and delivery has shifted the paradigm of radiotherapy to another level. It does not require any extra effort from the patient side as was the case during motion management with external gating devices such as active breath coordinator (ABC), RPM etc. The 4D imaging has facilitated real time motion management with a better resolution in space and time both.

  True 4D imaging can be achieved with integration of imaging device in treatment unit itself preferably a high-resolution CT/MRI. Halcyon unit by Varian with inbuilt megavoltage CT and Harmony model of LINAC by ELEKTA with integrated MRI head have given a solution for precise motion management. This will also help in adaptive treatment planning and delivery. Another solution would be to simulate a patient on biomechanical model having mechanical properties of different human tissues incorporated into it.

- **Synthetic CT:** In current era treatment planning is mostly based on CT scan data and electron density. Several sites have a limitation in treatment planning based on CT and hence fusion of MRI/ PET and CT images are done to have more information for further delineation and treatment planning which has its own limitations. Synthetic CT transpired as a solution where CT images are obtained by directly converting a MRI dataset in CT data set. It uses an algorithm for the conversion of MRI information in terms of CT gray scale which is directly connected to electron densities for dose calculation etc.

- **Artificial intelligence:** Use of artificial intelligence is now an area of interest for everyone including radiation physicist. This may create a revolution if used judiciously in coordination with medical physics. An algorithm with accurate electron density may use AI as a tool to delineate target volume as well as organ at risks automatically. At present this is utilized but needs manual intervention. Atlas based contouring tools are one of the utilizations of AI. The speed of a treatment planning system can also be enhanced with AI. There have been developments in this connection and a treatment planning system driven by AI was introduced in 2019. This created the on-board imaging based adaptive treatment plans. Artificial intelligence will have an impetus on whole radiotherapy process. Figure 2 represents a schematic infographic that how a large data set containing patient-, tumour- and treatment-related parameters can be processed to optimise risk-adapted radiation therapy dose distributions.

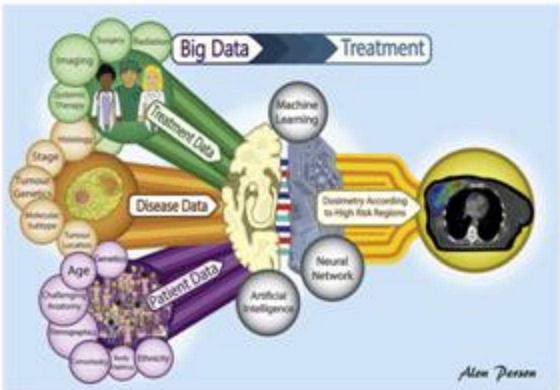


Figure 2: AI infographics Illustration made by Alon Person, using Adobe Illustrator cc 2019,

*Courtesy: Philip M.P. Poortmans, Silvia Takanen, Gustavo Nader Marta, Icro Meattini, Orit Kaidar-Person, Winter is over: The use of Artificial Intelligence to individualise radiation therapy for breast cancer, The Breast,Volume 49,2020,Pages 194-200

Summary

Medical physics in synergy with evolutions in information technology has revolutionized the diagnostic and therapeutic medicine. It is integrated and interwoven with the progressions in medical science and has provided new impetus in the past two decades. Cancer treatment and diagnostic armamentarium in medicine are unthinkable today without the input from medical physics. Artificial intelligence, machine learning and big data are the new horizons, which will modulate the benefit more appropriately to harness the benefit of newer researches for larger benefit of mankind. It has evolved as anew specialty and shaping the development in medical science with precision and seamless delivery of diagnosis and therapy.