Radiotherapy: An Update

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ABSTRACT
Radiotherapy is the art of using ionizing radiation to destroy malignant cells while minimizing damage to normal tissue. Radiotherapy has become a standard treatment option for a wide range of malignancies. Several new imaging techniques, both anatomical and functional are currently being evaluated as well as practiced for treatment planning of cancer. These recent developments have allowed radiation oncologists to escalate the dose of radiation delivered to tumors while minimizing the dose delivered to surrounding normal tissue. In this update, we attempt to pen down important aspects of radiotherapy.

Keywords: Radiotherapy, Megavoltage, Photon, Electron, Radioactive source, Fractionation.

INTRODUCTION
Ionizing radiation is used for both diagnostic and therapeutic purposes. The use of ionizing radiation for the treatment of cancer dates back to the late 19th century, remarkably soon after Roentgen discovered X-rays in 1895. The field of radiotherapy has undergone an amazing series of developments since its inception over a century ago.

Several recent advances have been made in radiation techniques, planning and delivery process like:
- Refinements in altered fractionation
- Three-dimensional conformal radiotherapy
- Intensity-modulated radiotherapy
- Charged-particle radiotherapy (protons, helium or neon)
- Neutron-beam radiotherapy
- Radioimmunotherapy
- Intraoperative radiotherapy
- Stereotactic radiosurgery.

PRINCIPLE OF RADIOThERAPy
The radiotherapy is based on the basic principle that rapidly proliferating cells are more sensitive to ionizing radiation compared to normal cells. Ionizing radiation deposits energy that injures or destroys cells by causing DNA strands to break and cross-link.

Though lethal dose for normal and abnormal tissues is almost same, normal tissues have greater ability to repair sublethal damage between doses of radiation than neoplastic cells.

THERAPEUTIC RATIO
Ionizing radiation does not distinguish between cancerous and normal tissues per se. Therefore, successful radiotherapy treatment depends on optimizing the dose to the tumor and minimizing damage to normal tissue, a delicate balance called the therapeutic ratio (Neal and Hoskin 1997).

Maximizing this ratio is the goal of oncology.

METHODS OF DELIVERY OF RADIOThERAPy
There are three major modalities of radiation therapy:
- Teletherapy or external beam radiation
  - Brachytherapy
  - Radioactive isotopes.

TELEThERAPy/EXTERNAL BEAM RADIATION
This is the most common modality accounting for 90% of radiation therapy. It involves the delivery of electromagnetic radiation (e.g. X-rays, gamma rays) or particulate radiation (e.g. electrons, protons) from a linear accelerator or radionuclide source, such as 60cobalt kept at a distance away from the patient. It is of two types depending on energy of rays, which are used for this purpose.

Kilovoltage Therapy
- Superficial X-rays (50-150 kV)
- Orthovoltage X-rays (150-300 kV).

Megavoltage Therapy
- Cobalt gamma rays (1.17-1.33 mV)
- Linear accelerators (4-25 mV) (1 mV = 1000 kV).

KILOvoltage THERAPy
Early radiotherapy was very limited due to devices that could produce only low energy X-rays (100 kV). By 1913 William Coolidge, an American physicist developed hot-cathode X-ray tubes, which produced energies in 200 kV range. Treatment with these tubes was initially termed Deep Roentgen therapy and later called orthovoltage XRT. It was used to treat superficially situated skin tumors.

Advantages
- The machinery was relatively inexpensive.
- It was simple in design.
- It demonstrated straightforward principles of operation.
MEGAVOLTAGE THERAPY

Chronological Development

1932 is considered as the starting of the megavoltage era due to the development of 1 megavolt van de Graaff generator. In 1943, the Betatron (a specific type of megavoltage unit) was developed by R Wideroe and DW Kerst. In 1950s, Isocentric 60Cobalt units were introduced. In 1952, the first stationary linear accelerator (8 mV) was installed in London. In 1956, Varian associated produced the first low energy isocentric linear accelerator. 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.

60COBALT UNITS

This unit has a 60Cobalt source surrounded by protective shielding with a shutter system, which allows the patient to be treated through an adjustable collimator. 60Cobalt is an isotope produced by bombarding, its stable form 59Co with neutrons. 60Cobalt then attempts to gain stability by the emission of gamma rays of 1.17 mV to 1.33 mV. It has decay half life of 5.26 years. Hence, the treatment times have to be adjusted monthly.

Advantages

i. 60Cobalt units were the first machines that delivered the dose maximum below the skin surface of the patient resulting in dramatically reduced skin reactions.
ii. It requires less servicing than a linear accelerator, except only monthly calibration.
iii. The relatively low cost has made them the favored source.

Disadvantages

i. The unit cannot be turned off.
ii. It should always be kept shielded.

LINEAR ACCELERATOR

Formally, it was known as electron linear accelerator in reference to the particle that is accelerated. In an accelerator, electrons produced from an electron gun are injected into a waveguide in synchrony with a radiofrequency wave produced from a magnetron. The electrons are accelerated to high speeds in the waveguide and are then fed into the head. Depending upon the components of treatment head either X-ray or electron beam is produced. These machines normally operate at 4 to 25 mV range.

Advantages

i. It has sophisticated computerized treatment delivery system.
ii. It can deliver tumoricidal doses of radiation to customized treatment volumes in any anatomical site.

Disadvantages

i. It is expensive to maintain than cobalt units.
ii. It requires daily calibration.

Linear accelerators have replaced 60Cobalt for the following reasons:

i. Variable dose rates.
ii. Enhanced skin sparing in comparison to 60Cobalt units.
iii. Multimodalities available in same treatment machine.
iv. A narrower penumbra than that produced by 60Cobalt units.
v. 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. The prefix ‘brachy’ simply mean a short range delivery of radiation. The National Council on Radiation Protection (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. Sources suitable for brachytherapy use consist of small amounts of radionuclide which are totally encapsulated by a non toxic 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 isotopes are Radium226, Cesium137, Iridium192 and Iodine125. Generally a dose of 65 Gy over 6-7 days is given when it is used as the sole treatment.

Advantages

i. A high dose of radiation can be delivered directly to the tumor sparing surrounding normal tissue.
ii. Treatment time is short.

Disadvantages

i. It can be used only in selected cases especially in the early stage of disease at accessible sites.
ii. It requires anesthesia and excellent expertise.
iii. It is an invasive procedure.

Types of Brachytherapy

a. Interstitial Brachytherapy: In this, radioactive sources are inserted into the tumor via surgical intervention. For example, in carcinoma of tongue and buccal mucosa.

b. Mold Therapy: The radiation source is placed into a plastic mold on the patient’s skin or mucous membrane. The radiation dose from a mold falls off rapidly and is therefore ideal for treating superficial tumors. For example, carcinoma of hard palate and skin cancer.

c. Intracavitary Brachytherapy: Radioactive isotopes are kept inside a body cavity. For example, carcinoma of nasopharynx and cervix, oesophageal and lung tumors.

Techniques for Brachytherapy

Depending upon the loading, brachytherapy is classified into preload and afterload techniques.

Preload Technique

Earlier the intracavitary sources were live radium sources, which were directly handled by the staff producing significant exposure...
to the radiotherapist, theater and nursing staff. $^{226}$Radium was favored mainly for its very long half life of 1620 years. However, it had numerous disadvantages and hence now a days, caesium is commonly used.

**After Load Technique**

It was introduced in the 1960s to overcome the disadvantage of preload technique. It may be conventional (manual) or remote (automatic).

**Conventional (Manual) Afterloading**

First hollow metal or plastic tubes are inserted into the tumor. The radiograph is taken to verify the position of the tubes and if the position is correct then only sealed radioactive sources are inserted into the tube manually.

**Remote (Automatic) Afterloading**

The plastic tubes are positioned within the patient as described above but source transfer is then conducted automatically with the help of machine. After the treatment, the source goes back into the machine.

Brachytherapy may be administered using high-dose rate (HDR- 1200 or more cGy/hr), medium-dose rate (MDR-200-1200 cGy/hr) or rarely, low-dose rate (LDR-40-200 cGy/hr) equipment.

**High Dose Rate (HDR) Afterloading Equipment**

The HDR system tends to contain a single active source, most commonly $^{192}$Iridium, which moves in steps to preprogramed positions. Typical active source is 1 mm in diameter and 4 mm in length. This is soldered to a stainless steel cable, which is mechanically driven in and out of the applicator.

**RADIOACTIVE ISOTOPES**

Radioisotope is either injected or taken as a drink to treat tumors. Commonly used isotopes are Iodine-131, Phosphorous-32, Yttrium-90.

**Fractionation in Radiotherapy**

The earliest treatments were generally delivered as single large exposures, by placing low-energy cathode ray tubes or radium-filled glass tubes in close proximity to tumors. The result was extensive normal tissue damage with rare incidence of cure of tumors. Fractionation of the total dose of radiation helps in minimizing normal tissue reaction.

**Conventional Fractionation**

For a given degree of tumor-cell killing, the delivery of multiple small doses of radiation (fractionation) carries lower risk of late complications than delivery of a single large dose. For this reason, fractionation has been a cornerstone of radiotherapy since the 1920s. Conventional fractionation is the application of 180 to 200 cGy in single daily dose and five fractions per week to a total dose of 40 to 70 Gy (4-7 weeks) depending upon the type of tumor (1 Gy = 100 cGy).

**Hyperfractionation**

In this two or more fractions of radiotherapy dose (115-120 cGy) are given per day with overall treatment time similar to that of conventional fractionation. Hyperfractionation helps in increasing the total dose without increasing the late reactions. Fractions are separated by atleast six hours, based on the biological observation that most sublethal damage repair occurs within six hours. For example, if two fractions are given per day, then $240 \times 5 = 1200$ cGy/week and hence total dose of 48 to 84 Gy (4-7 weeks) depending upon the type of tumor.

**Accelerated Fractionation**

It refers to delivering the same total dose over a shortened treatment time, most often through the use of twice or thrice daily fractions. It is done in an effort to reduce the repopulation of tumor cells (tumor-cell regeneration) in rapidly proliferating cancers. For example, if two fractions are given per day then $400 \times 5 = 2000$ cGy/week and hence total dose of 40 to 70 Gy (2-3.5 weeks) depending upon the type of tumor.

**Concomitant-boost Technique**

It is a variant of accelerated fractionation wherein 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.

**Accelerated Hyperfractionation**

This hybrid regimen incorporates features of both accelerated fractionation and hyperfractionation.

**Technological advances in Radiotherapy**

Two-dimensional (2D) radiotherapy consisted 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”. In conventional radiotherapy because of close proximity of head and neck tumors to critical organs like spinal cord, eyes, optic chiasma, etc., quite often delivery of maximal dose to tumor is not feasible. Advances in computer and imaging technology [CT/MRI/ 18-F-Fluorodeoxyglucose (FDG)-PET] have facilitated delivery of higher dose to the tumor, sparing critical organs. Advances in our ability to shape and modify intensity of radiation beams (fields) 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 (20 to 80 pairs of tungsten leaves) located in the head of linear accelerator. Each leaf within an MLC is robotically controlled and moves independently of the others to create computer-controlled beam shapes.

**3D Conformal Radiotherapy (3D-CRT)**

With 3D-CRT, sophisticated computer programming is used to determine the optimal beam shape and field arrangement. In addition, the multileaf collimator allows for the collimation of the X-ray beam during treatment. The tumor and regions at risk for
microscopic extension are contoured on each axial computed tomograph. The tumor volume is then visualized in three dimensions. A physicist and dosimetrist work together to construct a beam arrangement that will deliver the desired therapeutic dose to the tumor volume while minimizing the amount of radiation to the adjacent normal tissues.

Disadvantage
Movement of patients and tumors as a result of voluntary and visceral motion such as respiration and digestion presents significant problems.

The next direction in radiation oncology is to account for this movement and is being called four-dimensional (4D) conformal radiotherapy (CRT), a logical progression from 3D CRT.

Intensity-Modulated Radiation Therapy (IMRT)
Intensity modulated radiotherapy is the most advanced form of conformal radiotherapy. The underlying concept of IMRT was described as early as 1978, but due to the hardware and software needed, to implement, it was not widely available until the late 1990s. The beam intensity patterns of IMRT are so complex that a different type of treatment planning algorithm was designed called inverse planning. With this method, the radiation oncologist prescribes the treatment dose for a target volume and defines the allowable doses that surrounding normal structures can tolerate. The computer then performs repeated iterations to optimize beam intensity profiles and desired dose distributions. IMRT differs from 3D-CRT; in that each X-ray beam is broken up into many "beamlets", and the intensity of each beamlet can be adjusted individually. Hence, each field may have one or more areas of high intensity radiation and any number of lower intensity radiation, thus allowing for greater control of dose distribution with the target.

Rationale for IMRT in Head and Neck
The head and neck is an ideal site for IMRT due to the complex geometry of this area and the severity of radiation-associated toxicity. The toxicity from head and neck radiotherapy is among the worst seen in the field. The obvious advantages associated with sparing salivary glands have pushed intensity modulated radiotherapy in standard treatment of head and neck cancer faster than other cancer sites.

Charged-particle Radiotherapy
Although photon and electron beams are the primary modalities in radiation oncology, particle beams such as protons and heavy ions like helium or neon have also been developed for cancer treatment. There is also clinical interest in heavier charged particles like carbon, which have a similar finite range in tissues as protons but have a higher relative biological effectiveness (RBE) than protons. Charged-particle therapy has not gained much popularity since there is only a limited number of indications (For example, unresectable skull base and cervical spine tumors).

Protons Beam Therapy
The majority of patients receiving charged particle therapy have been treated with protons. Due to its unique energy absorption profile in tissues, proton beam therapy is one of the highly conformal radiation modalities. 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 proton beam, Bragg peak can be positioned 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. Smaller and more affordable cyclotrons are now in development, and if successful, this may result in the more widespread availability of proton-based radiotherapy in the coming decades.

Neutron Beam Therapy (Fast Neutron Therapy)
It is a specialized form of external beam radiation therapy that uses neutrons, which are much heavier than photons. A particle accelerator accelerates protons, which are deflected by magnet to a target, which creates the neutron beam. Cancer cells that are hypoxic or that are in certain stages of the cell cycle or that are proficient at repairing damage are relatively resistant to being killed by photon or electron beam irradiation. Such cells are less resistant to be killed by neutron beams because neutron (high LET radiation) produces much denser ionization inflicting relatively greater injury to malignant tissues compared with photon and electron irradiation (low LET radiation.)

Neutron beam therapy has been employed mainly for the treatment of inoperable, unresectable or recurrent salivary gland tumors. The safety and efficacy of the use of neutron therapy for the treatment of other forms of cancer has not been proven.

Advantage
Because of the high biological effectiveness, a full course of neutron therapy is delivered in only 10 to 12 treatments, compared to 30 to 40 treatments needed for photons and electron irradiation.

Disadvantages
i. It causes more normal tissue damage than photon therapy.
ii. There is clinical difficulty in generating neutron particles.

Radioimmunotherapy
It is a recent advance in cancer treatment that combines two types of therapies—radiation therapy and immune therapy using monoclonal antibodies. Monoclonal antibodies are immune proteins made in the laboratory to target and attach to a special part (an antigen) of the surface of a cell. In radioimmunotherapy radiation-emitting molecules (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. Radioimmunotherapy is being studied in several cancers, but has shown the most promise in the treatment of blood cancers, such as leukemia and lymphoma.

Advantages
i. Therapy can be completed quickly, usually in one or two treatments.
ii. It can minimize the risk of radiation damage to healthy cells.
Disadvantage
It may be complicated by anaphylactic reactions during and following infusions.

Intraoperative Radiation Therapy (IORT)\(^1\)
A single large dose of radiation is delivered in the operating suite after the tumor bed and adjacent normal organs have been defined. IORT typically involves the administration of electrons rather than photons. With electrons, the dose of radiation falls off rapidly with depth, and the physician is thus able to spare normal underlying tissues. The typical dose of IORT is 12 to 20 Gy in a single delivery.

Stereotactic Radiosurgery
It provides the precise delivery of a single large dose of radiation to a target that typically measures less than 3.5 cm in diameter. The procedure can be administered by a linear accelerator, gamma knife or cyclotron. By limiting treatment to a small target, the physician can ensure a steep fall-off in the amount of radiation that is administered to adjacent normal tissue. Stereotactic radiosurgery has been used to treat skull base tumors and nasopharyngeal carcinomas.\(^1,19\)

SUMMARY
In the past 20 years, the technological advances in radiotherapy have been immense which have improved effectiveness, decreased complications and expanded implications of radiation therapy; but some of the technology has not been rigorously evaluated. Although, the promise of new imaging modalities is great, it is not without its hurdles. Importantly, there are large financial and educational barriers in the initial setup and implementation of these new modalities.

REFERENCES