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Review Article

Evolution of Radiotherapy- A Brief Review

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Abstract
Beginning with the discovery of X-rays by Wilhelm Conrad Röntgen in 1895 and the subsequent application of X-rays for cancer treatment in 1896, the narrative unfolds through the advancements in radiation therapy modalities.
The discussion covers External Beam Radiotherapy (EBRT), including various techniques like 3D-CRT, IMRT, IGRT, stereotactic radiotherapy, and proton therapy. Emerging technologies such as Tomotherapy, Stereotactic Radiosurgery (SRS), Boron Neutron Capture Therapy (BNCT), Carbon Ion Therapy, and Brachytherapy are explored, offering tailored approaches for different cancer types.
The article delves into the history and advancements of brachytherapy, highlighting its techniques like intracavitary, interstitial, and HDR surface mould brachytherapy. The continuous pursuit of precision, efficacy, and reduced side effects in cancer treatment is evident throughout the narrative.
The article emphasizes the crucial role of radiation therapy, employing various ionizing radiation types, in targeting and eradicating cancer cells while minimizing harm to normal cells. The ongoing quest for advancements in technology and techniques reflects the commitment to improving cancer treatment outcomes. This article provides a comprehensive overview of radiation therapy's historical evolution and current state in cancer treatment
Keywords: *Radiotherapy, EBRT, Brachytherapy, IMRT, SRS, IGRT, Proton therapy.*

Introduction

Cancer is one of the major killer diseases in humans whose origins are not yet well established despite extensive research in different international laboratories and hospitals all over the world.[1] Radiation therapy uses a beam of radiation to target and destroy cancer cells in a specific body area while minimizing damage to normal cells. Radiation can cause different types of damage to the DNA, cell cycle, chromosomes, and survival of cancer cells, making them unable to grow and spread. Normal cells can usually repair themselves after radiation exposure.[2] About 66% of all cancer patients receive radiation therapy as a sole or combined treatment option.[3] Radiation therapy has evolved with advances in engineering and computing, leading to more precise and conformal techniques that can deliver higher doses of radiation to the tumour.[4]

The mechanism behind killing the malignant cells is through high-intensity ionizing radiation breaking down the DNA of the target cell through direct or indirect interaction with the radiation. The radiation can indirectly damage the cells' DNA by creating free radicals from water molecules in the cells. Free radicals are very reactive and can cause structural changes in the molecules they interact with. Most of the radiation damage is due to the indirect effect. However, radiation can also harm normal cells, an unwanted side effect. The advantage of radiation therapy is that normal cells can repair themselves, while cancer cells cannot.

Different types of radiation, such as X-rays, γ-rays, α-particles, protons and heavy ions, are used in radiation therapy. They are produced by different machines, such as Telecobalt, Medical Linear Accelerator (Medical LINAC), Cyclotron and Synchrotron. Radiation therapy has evolved, and new techniques have been developed. This article will briefly overview the history and current state of radiation therapy.

History

X-rays were discovered by Wilhelm Conrad Röntgen in 1895 when he observed a fluorescent screen glowing near a cathode ray tube. He realized the tube emitted invisible rays that could penetrate objects and reveal their internal structure. He took the first X-ray image of his wife's hand, showing her bones and ring. Soon after, X-rays were used to treat the first cancer patient with a breast tumour in 1896 by E.H. Grubb at the suggestion of Dr Ludlam [5]

Subsequently, radioactivity was discovered by Henri Becquerel in 1896 when he noticed that uranium salts emitted radiation without any external source. He studied phosphorescence, the emission of light by some materials after exposure to light or radiation. His discovery led to further research by Marie and Pierre Curie, who isolated the radioactive elements polonium and radium and advanced the knowledge of radioactivity.[6]

Radiotherapy is classified into two types:

External Beam Radiotherapy (EBRT)

EBRT is a non-invasive way to treat cancer patients. It uses special equipment that emits radiation beams at the exact spot where the cancer cells are. The machine moves around the body and delivers radiation from different angles to a fixed point called an isocentre[7]. EBRT has been applied to various types of cancer, and its techniques have evolved[8].

In 1913, Coolidge invented the "hot cathode" X-ray tube, which is still used in most diagnostic X-ray centres. Until around 1950, most EBRT treatments used X-rays generated at up to 300 kV voltages.[9] These machines were classified by their kilovoltage range.

Subsequent development of higher-energy machines and the increasing popularity of the cobalt-60 units in the 1950s and the 1960s resulted in a gradual demise of the conventional kilovoltage machines.

In 1953, the Medical LINAC was used to treat patients for the first time in London, marking the beginning of the use of this device in clinical treatment.[9] Medical LINAC is the most dominant radiotherapy machine with the most advanced treatment techniques for cancer patients.[10]

EBRT includes 3-dimensional conformal radiotherapy (3D-CRT), Intensity/Volumetric-modulated radiotherapy (IMRT/VMAT), stereotactic radiotherapy (SRT), image-guided radiotherapy (IGRT), proton and heavy ion beam therapy, etc., with each modality having specific advancements and adaptation for the tumour type.

Three-Dimensional Conformal Radiotherapy (3D-CRT):

3D-CRT is based on 3-D anatomic information and uses treatment fields that conform as closely as possible to the target volume to deliver an adequate dose to the tumour and the minimum possible dose to the normal tissue.[11]

3D-CRT conforms to the required anatomical shape using a motorized multi-leaf collimator (MLC) resembling the Beams Eye View (BEV). It uses a planning method with a trial-and-error method from different angles and shapes, which decreases the treatment margins and minimizes the volume of normal tissue receiving a clinically significant radiation dose. The 3-D treatment planning system (TPS) calculates the dose.[12]

To perform 3D-CRT planning, an accurately defined target must be based on radiographic or functional imaging. Rigid immobilization allows a reduction of margin around the target, resulting in a reduced dose to the surrounding normal tissue and ensuring that the prescribed dose is accurately delivered to the planning target volume (PTV). The increasing use of multiple radiation beams, with many potentially out of the axial plane, further emphasizes the need for good immobilization.[13]

Intensity Modulated Radiation Therapy (IMRT):

IMRT refers to a radiation therapy technique in which a non-uniform fluence is delivered to the patient from any given position of the treatment beam to optimize the composite dose distribution.[11] Using a LINAC and a three-dimensional TPS, this technique is most commonly used in many centres. It is highly conformal and precise compared to the 3D-CRT, possibly reducing late toxicity and increasing the delivered dose for better tumour control and survival.[14]

After the introduction of 3D-CRT, inverse planning was introduced in 1982[15], and then IMRT became the most important and standard radiotherapy modality. The two main key features of IMRT are non-uniform beam intensity of radiation beam and computerized inverse planning. These two features enable the development of a very complex plan, which is impossible in 3D-CRT.

Image Guided Radiation Therapy (IGRT):

IGRT relies on the built-in imaging system of a LINAC to target and administer radiation precisely. Various IGRT modalities involve acquiring patient anatomy images prior to treatment using techniques such as kV-kV/kV-MV planar imaging, kV-CBCT (Cone Beam Computed Tomography)/MV-CBCT, DIBH (Deep Inspiration Breath-Hold), and SGRT (Surface Guided Radiation Therapy). The obtained images are fused with the reference image used during the simulation. Among these modalities, kV-CBCT is particularly prevalent.

CBCT, developed in the late 1990s and integrated into clinical radiation therapy in the early 2000s, stands out as one of the most widely adopted tools in IGRT. A CBCT system scans the target from multiple projection angles and reconstructs a three-dimensional (3D) image from these projected images. This process is utilized by either the megavoltage radiation beam emitted by the LINAC or a kilovoltage beam delivered by an additional x-ray tube attached to the LINAC.[16]

Tomotherapy:

Tomo-therapy is a type of IMRT delivered in a fan beam, similar to a CT scan. The target is treated by dividing the total volume into slices. The gantry moves helically, rotating in 360^o, and the couch slides to and fro.

The first paper on Tomotherapy was submitted in 1992, but it took a year to be accepted. In the year 2001, the first clinical trial was observed.[17]

Stereotactic Radiosurgery (SRS)/Stereotactic Radiation Therapy (SRT):

Stereotactic Radiotherapy or Radiosurgery is an ideal treatment for medically inoperable early-stage small tumours with a local control rate of about 90%. Some forms of tumour motion management and image-guided radiation therapy are the prerequisites for the fulfilment of the goal to deliver a very high radiation dose to the tumour without overdosing on the surrounding normal tissues.[18] Cyberknife, Gamma Knife and LINACs with very tight isocentre and high-definition MLC are the ideal sources for this modality.

Stereotactic radiotherapy or radiosurgery is treated with the help of a stereotactic frame first described for neurosurgery by Horsley and Clarke in 1908. Much literature was documented on this topic in the early 19th century.[19]

Proton Therapy:

Employing protons in medical treatment was first suggested in 1946, and the first attempt was made in 1954 at the University of California Lawrence Berkeley Laboratory. In 1990, a dedicated proton medical device featuring a gantry system started the official application of proton therapy at Loma Linda Medical Centre. The second proton therapy centre was opened at MGH in 2001. Gradually, it was accepted after many clinical trials and equipped with integrated 4-dimensional CT and IGRT. However, many clinical trials and studies are still related to tumour motion and dose distribution.[20]

Boron Neutron Capture Therapy (BNCT):

Locher proposed the principle of Boron Neutron Capture Therapy in 1936. The initial attempt to perform it on a patient occurred in 1951 when a person diagnosed with Malignant Glioma underwent the procedure using the nuclear research reactor available at the Brookhaven Graphite Research Reactor. Subsequently, BNCT was carried out in 40 patients, but severe side effects were reported. In 1968, Hiroshi Hatanaka in Japan reinstated the clinical application of BNCT with impressive results, achieving a survival rate of 58% over five years. Gradually, BNCT gained traction in limited countries equipped with research reactor facilities capable of delivering an epithermal neutron beam. [21, 22]

Carbon ion therapy:

Carbon ion therapy is an ion beam therapy used in cancer treatment, categorized under particle therapy. It falls under the high Linear Energy Transfer (LET) radiation classification, resulting in dense ionization along its path. This therapy demonstrates a distinct energy distribution in depth called the 'Bragg Peak.' Treatment with carbon ions offers several physical and radiobiological advantages. The treatment planning process for carbon ion therapy is similar to proton beam therapy, with the main difference lying in the variability of Relative Biological Effectiveness (RBE). The first instance of carbon ion therapy was conducted by the National Institute of Radiological Sciences in Japan in 1994, where over 9000 patients with various types of tumours received treatment. Numerous studies are ongoing to investigate the benefits of using charged particles for cancer treatment.[23]

Brachytherapy

In brachytherapy, in contrast to EBRT, the source is a radioisotope that can be positioned inside or near the tumours temporarily or permanently. The radioisotope emits low-energy gamma radiation that protects the other organs near the tumour and delivers an extremely high dose to the tumour. In brachytherapy, radioisotopes are produced artificially as seeds or capsules.[24]

In 1903, the first gynaecological brachytherapy was described by Margareth A. Cleaves in New York. A patient with inoperable cervix uteri cancer was treated with 700 mg radium bromide put into the glass tube. In 1911, the first prostate cancer treatment was reported with brachytherapy by Pasteau, who administered radium via a temporary urethral catheter.[25] Several artificially created radioactive nuclides exist, considerably outnumber the non-radioactive ones created today. The Nobel Prize for Chemistry in 1935 was awarded jointly to Frédéric Joliot and Irène Joliot-Curie "in recognition of their synthesis of new radioactive elements." In the decade after World War II, radioisotopes such as cobalt-60 (Co-60), gold-198 (Au198), tantalum-182 (Ta-182), and cesium-137(Cs-137) were introduced and became the radionuclides of choice in intracavitary therapy, replacing radium-226. In 1958, iridium-192 (Ir-192), which replaced these sources, was first used clinically by Ulrich Henschke at the Memorial Sloan Kettering Cancer Centre.[26]

Brachytherapy techniques are classified according to the radiation exposure and source position relative to the tumour and dose rate.

Different applications are used to place the radioisotopes in the required position. According to the application, brachytherapy is categorized into intracavitary, interstitial and surface mould brachytherapy.

Intercavitary brachytherapy:

This type of radiation is used to treat cavitary areas, like the cervix. An applicator is placed in an operating room area before the actual source insertion. In the case of the cervix, applicators like tandem or ovoid are used.[27]

Interstitial brachytherapy:

Interstitial brachytherapy began in 1917 when Barringer inserted radium needles transperineally into the prostate, guided by a finger in the rectum.[30] In 1922, Geoffrey Keynes used 'interstitial radium needles' to treat breast cancer in palliative. He achieved a surprising disease control in cancer confined to the breast with a three-year survival rate of 83.5%.[29] Interstitial brachytherapy initially used radium needles implanted in superficial tumours. However, other radioactive nuclei were also developed over time. The implant system developed by Manchester and Quimby is still followed today. Low dose rate (LDR) ribbons of ^{192}Ir or ^{137}Cs were the most popular devices for interstitial brachytherapy until remote high dose rate (HDR) after loaders were developed.[28]

Surface mould brachytherapy:

HDR surface mould brachytherapy was first introduced by Joslin to treat skin lesions, followed by the discovery of radium. It is a non-invasive process. Applicators are placed on the top of an individually constructed patient mask. A soft silicone rubber applicator is also used on a flat area up to 24cm. Jolly and Nag reported on the use of dental moulds for the treatment of head and neck cancers.[29]

Future Recommendations

In the coming years, the evolution in radiotherapy technology is expected to be driven by advancements in artificial intelligence, machine learning, and quantum computing, marking a paradigm shift in the field. With more research and development, artificial intelligence is predicted to significantly reduce the workload of radiotherapy personnel, including radiation oncologists, medical physicists, and radiotherapists.

Conclusion:

Radiation therapy, a crucial cancer treatment, utilizes various types of ionizing radiation to target and eradicate cancer cells while minimizing damage to normal cells. The history of radiation therapy dates back to the discovery of X-rays by Wilhelm Conrad Röntgen in 1895 and the subsequent use of X-rays to treat cancer in 1896. Over the years, technological advancements have led to different modalities within radiation therapy, such as External Beam Radiotherapy (EBRT), including 3D-CRT, IMRT, IGRT, SRS/SRT, and proton therapy. Emerging techniques like Tomotherapy, Stereotactic Radiosurgery (SRS), Boron Neutron Capture Therapy (BNCT), and Carbon Ion Therapy offer tailored approaches for various cancer types. Brachytherapy, utilizing radioisotopes placed inside or near tumours, has evolved with applications like intracavitary, interstitial, intraluminal and surface mould brachytherapy. These advancements reflect a continuous quest for precision, efficacy, and reduced side effects in the battle against cancer.

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