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Original Research

Radiation Therapy of Cancers, X-Ray Beams, Therapeutic Photon Beams, and Brachytherapy Application Techniques

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Abstract:

One physical agent that can kill cancer cells is radiation. The radiation is referred to as ionising radiation because it deposits energy into the cells of the tissues it travels through by creating ions, which are electrically charged particles. Cancer cells can be killed by this stored energy or by genetic alterations that lead to cancer cell death. The suggested hallmarks of cancer growth and treatment have been the subject of tremendous advancement in recent years. Nevertheless, cancer's rising prevalence makes its therapeutic care an ongoing issue in the modern day. Some of the methods used to treat this condition include hormone therapy, immunotherapy, radiation therapy, surgery, and chemotherapy. Radiation therapy is still a vital part of cancer treatment; it's used by about half of all cancer patients and accounts for 40% of cancer treatments that are successful in curing the disease. Radiation therapy primarily targets cancer cells by destroying their ability to divide. The United Kingdom has declared 2011 the Year of Radiation Therapy to commemorate one hundred years of progress in the field since Marie Curie's radium discovery earned her the Nobel Peace Prize. Radiation oncology has come a long way in the previous century, with new procedures and a better understanding of cancer cell reactions to radiation. Both of these things will hopefully lead to better survival rates and fewer side effects for cancer patients undergoing therapy.

Keywords: Radiation Therapy, X-Ray, Therapeutic Photon, Brachytherapy, Techniques

Introduction:

Around 41% of American males and females born today will get a cancer diagnosis during their lives. What this means is that 1,500,000 Americans have received cancer diagnoses in the last year. We still have a ways to go, however, despite the fact that cancer therapy science and

technology are continuously improving [1]. Overall, cancer patients have a much lower 5-year survival rate than the general population at 65% (though this varies greatly by disease type). Cancer claimed the lives of about 600,000 Americans in 2010. So, it's very evident that there's a pressing need for significant advancements in cancer prevention and treatment. Various nanotechnology-based radiation oncology applications are detailed in this volume, all with the common aim of bettering patient outcomes. Providing an overview of radiation therapy for cancer is the primary goal of this introductory chapter.

Wilhelm Roentgen and Becquerel both made discoveries on radioactivity and x-rays in the late 19th and early 20th centuries, but it wasn't until a year or two later that the first accounts of radiation's medicinal applications appeared (1897). Additionally, early accounts of radiation's harmful consequences surfaced; for example, Becquerel detailed the reddening and ulceration of his skin that happened when he accidentally left a radium container in his pocket. Consequently, skin toxicity has been a concern since the beginning. The goal of current treatment methods is to minimise kin toxicity while delivering radiation dose to deep tumours, as we will show later [2].

William Coolidge quickly created the "hot" cathode tube (1912–1913), despite the fact that early cathode-ray tubes were unreliable and only generated weak radiation. This improved apparatus could treat rather deep-seated tumours since it generated x-ray spectra with peak energies of 200-250 kV and the corresponding increased penetrating power. The modern x-ray tube may trace its lineage back to it. The utilisation of Cobalt-60 gamma sources for external beam treatments began in 1951, and medical linear accelerators (LINACs) with [3] megavoltage (MV) beams were introduced in 1952. This was followed in 1937 by the first treatment unit that used spectra with peak x-ray energy above 1 MV. These beams deposit their maximal dose some distance below the skin surface, allowing the treatment of deep tumours with fewer skin reactions. The progressive development of high energy treatment units was crucial for both this reason and the rise in penetrating power. The first commercially available multileaf collimators (MLCs) were mounted to treatment unit gantries in 1984. They are a collection of miniature, independently motorised collimator blades. In the 1990s, intensity-modulated radiation therapy (IMRT) was commercially developed, allowing the MLCs to move across the radiation field in order to regulate its intensity. This method has become the gold standard for many patients because it allows treatment planners to shape the dose distribution, meaning that they can deliver a high dose to the targets while minimising the dose to nearby tissues [3]. One solution to the lengthy treatment times caused by IMRT's complex fields is volume-modulated arc therapy (VMAT). In this method, the gantry spins around the patient while the MLCs move, cutting the beam-on time from 5-10 minutes to just 1-2 minutes. Below, you can find descriptions of protons and electrons, two other types of radiation utilised in radiotherapy. From its inception, radiation therapy has relied heavily on imaging. In the late 1960s and early 1970s, radiation therapy simulators were produced. These were kilovolt-age (kV) x-ray units designed to mimic the treatment machine's geometry.

In order to determine which organs would be exposed to radiation, doctors took pictures at the same angle as the therapy beams. For this reason, they were able to protect these organs using either generic or specifically designed radio-opaque blocks. Hounsfield invented computed tomography about this time, but regular CT-based treatment planning couldn't happen until the 1990s, when computers and related networks reached a certain level of sophistication. It is also common practice to supplement CT scans with other imaging modalities including positron emission tomography (PET) and magnetic resonance imaging (MRI) in order to better define tumour volumes.

For a long time, the treatment unit's MV x-rays were employed to create beams-eye view pictures of the treatment field on radiographic film.

Electronic portal imaging systems have mostly supplanted film. In addition, state-of-the-art LINACs have kV x-ray tubes and detectors mounted on the gantry, which provide excellent images for patient preparation. It is now standard practice in many clinics to take CT pictures daily to ensure appropriate patient positioning, and this configuration can also take these images. Radiation can be administered to patients in a variety of ways beyond only external beams. The method of brachytherapy, which comes from the Greek for "short distance," involves inserting sealed radioactive sources into or directly onto the tumour as an alternative. The majority of brachytherapy treatments employed radium at first [5], but numerous additional materials, including as Ir-192, Au-198, and I-125, were made possible with the 1934 discovery of artificial radioactivity. While external beam radiotherapy is the main focus of this work due to its prevalence in the field, nanotechnology has the potential to enhance the effectiveness of brachytherapy treatments as well.

X-Ray Energy:

Some materials allow x-rays to pass through them unaltered, whereas others attenuate them through absorption or scattering (Johns and Cunningham 1982; Hendee and Ibbott 2005; Khan 2007; Metcalfe et al. 2007; Podgorsak 2005). The attenuation coefficient, μ, and the thickness of an infinitesimally thin slab of material are directly related to the fractional number of photons attenuated by the slab. The distinct coefficients for different absorption and scattering effects are included in this coefficient. Because of their relevance to radiation-nanoparticle interactions, we provide a brief description of them in the following paragraphs.

Consistent dispersion. When x-rays are distributed coherently, they retain all of their energy. The process begins with an electromagnetic wave vibrating the atom's electrons, which in turn release radiation of the same wavelength. The scattered x-ray is the result of the merging of the released waves [5]. Since there is no energy deposition in the medium and the probability of this interaction is extremely low for high-energy photons interacting in soft tissue, it is irrelevant to radiation therapy. In diagnostic imaging, it contributes to patient scatter and, in turn, affects picture quality.

The phenomenon of photoelectric effect. When a photon interacts with an electron located inside a material, this phenomenon is called a photoelectric interaction. The contact causes an electron to be ejected from the atom, its kinetic energy being equal to the disparity between the incident photon's energy and the ejected electron's binding energy. Where Z is the atomic number of the medium and E is the photon energy, the mass attenuation coefficient for photoelectric absorption typically ranges as Z3/E3. This interaction process is most common for low-energy incident photons (<0.03 MeV) in soft tissue, but it is quite rare for the megavoltage energies employed in external beam radiation therapy. Bones, which have a relatively high Z, show a lot of contrast in diagnostic x-ray pictures because the photoelectric effect is Z dependent.

Using gold nanoparticles, which are discussed in later chapters, is one way this dependence might be utilised to enhance the radiation's therapeutic effect. Because gold has an atomic number that is over ten times more than soft tissue, adding gold nanoparticles enhances x-ray absorption and photoelectric effect electron release. Interactions on Compton waves [6]. At low x-ray energies, Compton interactions predominate in x-ray interactions with soft tissue; but, at higher energies, the photoelectric effect becomes dominant. The x-ray photon interacts with electrons that are relatively loosely bound in these interactions. Some energy is lost in scattering and some is gained by the electron, which is subsequently released from the atom, in every encounter. The probability of a Compton interaction diminishes gradually as the photon energy increases. The interaction probability is mostly determined by electron density and is nearly independent of atomic number since these interactions involve loosely bound electrons. This indicates that the radiation dose to tissues

downstream from bone is not significantly changed by its presence in the beam's path.

Making pairs. An x-ray absorption event is pair formation. This process takes place when an x-ray photon gets very near to an atom's nucleus and gets converted into mass as a positron-electron pair. This interaction can only take place if the incident x-ray has a minimum energy of 1.02 MeV, which is the mass equivalent of this pair (2 × 0.51 MeV). Any energy that goes beyond this point is split evenly between the two particles.

Features of Photon Beam Therapy:

The dose varies with depth. Although x-ray beam attenuation follows a form that combines exponential attenuation (as mentioned above) and 1/r2 fall-off with increasing source distance, the shape of the change in deposited dosage with depth in a medium is very different. When photons connect with tissues on the patient's surface, they release high-energy electrons that settle downstream and deposit their energy. More and more electrons are implicated at deeper and deeper depths, leading to an initial dose rise in the accumulation zone and then a maximum [6]. The term for this effect is the "skin-sparing effect" because deeper tissues receive a somewhat higher dose than the more delicate skin. Attenuation and the 1/r2 fall-off cause the photon fluence to decrease with depth. As a result, the density of electrons that deposit dosage decreases with depth, which eventually causes a fall-off in dose as one descends deeper.

Dosage administration. Using isodose curves—lines linking sites that receive the same dose—we can describe the structure of the dose distribution. In most cases, the dose is highly consistent throughout the middle of a wide beam. A uniform distribution is necessary for some newer LINACs due to their extremely non-uniform dose distributions [7], which can be altered with the application of beam modifiers, as will be explained later on. It is the geometric penumbra, collimation, and beam energy—the amount to which photons are dispersed in the forward direction—that determine the form of the dose distribution at the edges and outside the beam. The geometric penumbra is a result of the finite size of the LINAC's focus spot.

Electron Beams for Medical Treatment:

The media's electrons are triggered into motion when photons engage with it by photoelectric, Compton, or pair formation events, as mentioned before. Radiation dose is actually deposited by electrons, not photons. Another possible source of electrons is the LINAC itself; current LINACS may generate electron energies of 4–20 MeV or even higher. No matter where the electrons come from, as they move through the medium, they slowly lose energy until they can be grabbed by atoms. Collisions between electrons in atoms that are not elastic. Higher-Z materials typically have lower rates of energy loss due to the excitation or ionisation of atomic electron clouds because their electrons are typically more densely bound, a property that is dependent on electron density. The energy loss rate through water (or soft tissue) remains relatively constant at 2 MeV/cm for high-energy electrons (E > 1 MeV).

Because of this, we can tell how deep electron beams can go; for instance, if we irradiate a neck node with an 8-MeV beam, the spinal cord will only get a very little dosage if we go at least 4 cm deep. Atomic nuclei impact in an inelastic manner. When an electron approaches a nucleus, the nucleus's Coulombic field deflects and slows it down, resulting in Bremsstrahlung x-ray energy loss. A bremsstrahlung interaction is more likely to occur as the electron's kinetic energy and Z both increase. When high-energy electrons smash with the objects of diagnostic x-ray tubes and LINACs, high-energy photon beams are produced by this collision. High-energy photo- and Compton electrons undergo repeated Coulomb scatterings, causing them to travel through tissue in a twisted fashion. The scattering cross section is inversely related to the electron energy and roughly proportional to Z2.

Radioactive Agents in Cancer Treatment:

An Overview of Radioactivity:

Radioactivity occurs when a nucleus that is not stable enough to stay put emits particles and

gamma rays as it decays into a more stable neutron-proton structure. The sample's half-life is a measure of its degradation rate. Just think about it: that's how long it takes for half of the sample's atoms to decay. For example, Au-198 has a half-life of three days, whereas Ra-226's half-life is sixteen hundred twenty-two years. The various decay mechanisms of a nucleus are briefly described here.

Alpha Deterioration:

The nuclear stability is enhanced by alpha decay, which causes the nucleus to emit a single alpha particle. A helium nucleus consists of two protons and two neutrons. Large nuclei are the only ones that may undergo this disintegration. For a long time, it served as a therapeutic agent by decaying from Ra-226 to Rn-222; its half-life is 1622 years. As radon breaks down into stable lead, it releases a shower of gamma rays [8]. In cancer therapies, these photons were utilised to administer dose.

The Beta Decay Process:

In beta decay, the nucleus releases an electron, also called a beta particle, which can be positive or negative. A nuclear nucleus with an abnormally high neutron/proton ratio can undergo nuclear nucleus transmutation, increasing its atomic number. The emission of an electron occurs all at once. Beta particles are released in a continuous energy spectrum up to a decay-specific energy. Decomposition, in which a positive electron (positron) is emitted, may occur in a nucleus if the ratio of neutrons to proton is lower than what is required for stability. PET scans include linking a metabolically active substance to a positron-emitting isotope, such F-18. Two 511 keV photons, one going in the opposite way, are released when the isotope's positrons swiftly engage with tissue electrons, annihilating both the positron and the electron. Reconstructing the distribution of the metabolically active chemical is made possible by detecting these photons.

Radiation treatment methods:

One physical agent that can kill cancer cells is radiation. The radiation is referred to as ionising radiation because it deposits energy into the cells of the tissues it travels through by creating ions, which are electrically charged particles. Cancer cells can be killed by this stored energy or by genetic alterations that lead to cancer cell death. By damaging cells' genetic material (deoxyribonucleic acid, DNA), high-energy radiation prevents cells from dividing and multiplying [13]. While it's true that radiation can harm both healthy and cancerous cells, the point of radiation treatment is to target cancer cells specifically while exposing healthy cells either directly or indirectly to the lowest possible dose. The ability of normal cells to repair themselves and maintain their normal function state is typically greater than that of malignant cells. Differential cancer cell death occurs because cancer cells are typically less effective than normal cells at repairing damage caused by radiation treatment [9, 10]. Both curative and palliative radiation treatments are viable options for cancer patients seeking relief from the disease's symptoms. Combination tactics with other treatment modalities, such as immunotherapy, surgery, or chemotherapy, are additional indications for radiation therapy. The goal of radiation therapy, when administered before to surgery (neoadjuvant therapy), is to reduce tumour size. Radiation can eradicate any remaining tumour cells, no matter how small, when administered as adjuvant therapy following surgery. The fact that different types of tumours react differently to radiation therapy is common knowledge. The most frequent malignancies that are treated with radiation therapy are shown in Table 1. There are two methods for precisely targeting tumours with radiation. By directing high-energy rays (photons, protons, or particle radiation) onto the tumor's site, external beam radiation is administered from outside the body. In medical settings, this is the standard of care. Brachytherapy, also known as internal radiation, involves inserting radioactive sources—sealed in catheters or seeds—directly into the tumour location. Due to its short-lived effects, this is most commonly used for routinely treating gynaecological and prostate cancers, or when retreatment is necessary.

Fractionation:

Cancer and different normal tissues have different radiobiological characteristics, which is why radiation therapy is given in a fractionated regime. Because normal cells are better able to repair radiation damage below the fatal threshold than cancer cells, these regimes tend to increase the survival advantage of normal tissues over cancer cells. Since normal cells divide at a slower rate than cancer cells, they have more time to fix damage before replicating. Early studies on fractionated radiation therapy's effects in the 1920s paved the way for the creation of regimens that compared various treatment plans according to total dose, fraction number, and total treatment time [11–14]. The linear-quadratic formula, which takes into account the time-dose variables for different types of tumours and healthy tissues, is the basis of current regimes [15]. Nowadays, radiation treatment often involves doses ranging from 1.5 to 3Gy administered daily for a few weeks.

The Third Dimensional Conformal Radiation Therapy (3DCRT):

Because 3D radiation therapy based on CT imaging permits exact identification of the tumour and key normal organ structures for optimal beam placement and shielding, it has largely superseded 2D radiation therapy employing rectangular fields based on plain X-ray imaging. The goal of radiation delivery is to reach the gross tumour volume (GTV), adding a margin for microscopic tumour extension (CTV) and an additional margin for uncertainty caused by organ movements and setup changes (PTV) [16].

Radiation treatment with a targeted intensity level:

By using IMRT, the oncologist can avoid vital organs while tailoring radiation doses to the tumor's unique structure. Computer-controlled intensity-modulation of several radiation beams throughout treatment and inverse planning software are the two main components of IMRT. The use of linear accelerators equipped with static or dynamic multi-leaf collimators, as well as tomotherapy equipment, has made IMRT accessible in numerous therapeutic departments. Because of this, the treatment ratio for several tumour locations has improved, including malignancies of the head and neck [17], prostate [18], and gynaecological [19].

Image-guided radiation therapy (IGRT) The risk of missing a tumour owing to organ movement or alterations in patient setup increases as treatment margins get tighter and more conformal [20]. Even a little misalignment can cause unintended radiation exposure to healthy organs when vital tissues are located near the tumour. By utilising data collected from pre-radiotherapy imaging, IGRT enables the identification and rectification of such inaccuracies. Daily cone-beam CT images obtained before to each treatment are one example of this [21]. The therapeutic ratio for several tumour sites, including head and neck cancers [23] and prostate cancers [24], has been improved thanks to the increased precision, which has made dose escalation possible [22].

The SBRT stands for stereotactic body radiation therapy.

Due to the aforementioned technical developments, SBRT is now possible to ablate tiny, well-defined primary and oligometastatic tumours anywhere in the body by precisely delivering extremely high individual radiation doses over a short number of treatment fractions [25, 26]. Any nearby healthy tissue is at risk of radiation damage as a result of the high dose. In contrast, there is no clinically relevant damage because the percentage of normal tissue in the high dosage zone is tiny and non-eloquent [27]. When it comes to treating early stage non-small cell lung cancer in patients who aren't surgical candidates, SBRT has demonstrated remarkable efficacy. Some other types of tumours include those in the spinal cord, pancreas, oligometastases, hepatic, renal, head and neck, and prostate [28, 29, 30].

Photon radiation (x-rays and gamma rays) is the most common form of radiation utilised in cancer treatment.

Photon beams are extremely light and have a negligible amount of radiation charge. Photons such as X-rays and gamma rays are commonly employed in radiation therapy for the treatment of different types of cancer. Sparsely ionising electromagnetic radiations such as X-rays and gamma rays are constituted of photons, which are massless particles of energy. Gamma rays come from the disintegration of radioactive elements like cesium, cobalt-60, and radium, while X-rays are produced by devices that excite electrons, such as cathode ray tubes and linear accelerators.

Cell Death: Classification and Features:

Radiation therapy, like to other anticancer treatments, kills cancer cells by triggering several forms of cell death [37]. It takes time for radiation therapy to eliminate cancer cells. Before cancer cells begin to die, radiation therapy takes hours, days, or weeks. Once cancer cells begin to die, they continue to die for weeks to months after radiation therapy finishes.

One of the main cell death mechanisms used in cancer therapy, and radiation therapy in particular, is programmed cell death, or apoptosis [38–40]. Cell death and the development of apoptotic bodies are hallmarks of the cell death process. The significance of mitochondria in apoptotic cell death is significant [41]. Condensed chromatin, nuclear margination, and DNA fragmentation are common causes of cellular blebbing. Apoptotic cells typically keep their cell membranes intact. One key component of radiation therapy's effectiveness is its ability to induce cell death in cancer cells [42].

Cell death that happens during or after abnormal mitosis (cell division) is called a mitotic catastrophe. It happens when chromosomes are mis-segregated, which causes large cells with abnormal nuclear morphology (many nuclei). Micronuclei and centrosome overduplication are common in cells [43, 44]. Abnormal mitotic events account for the vast majority of solid tumour cell death following irradiation [45]. Ionising radiation causes cell death primarily through the two pathways described above.

When cells undergo necrosis, their membranes rupture, causing them to enlarge dramatically. Vacuolization, non-condensed chromatin, and disintegrating cellular organelles are hallmarks of abnormal nuclear shape, which is accompanied by enlargement of the mitochondria and rupture of the plasma membrane, which in turn causes the loss of intracellular contents [46]. While radiation-induced necrosis is rare, it can happen in cancer cell lines and tissues.

The inability of cells to divide and multiply over time is known as senescence. Senescent cells are still functional, but they no longer divide, stop making new DNA, and eventually flatten out and expand. They also become more granular. After radiation therapy causes DNA damage and other forms of cellular stress, cancer cells reportedly undergo senescence and ultimately perish mostly by apoptosis [47, 48].

The process of autophagy has only been described very recently. Radiation causes this type of cancer cell death. The autophagic/lysosomal compartment is involved in autophagy, a genetically controlled type of programmed cell death in which the cell digests itself. It is defined by the sequestration of organelles like ribosomes and condensed nuclear chromatin by the creation of double-membrane vacuoles in the cytoplasm [49, 50]. According to reports, many forms of radiation-induced cell death include diverse sets of genes and intracellular processes. The ATM-p53-Bax-Cytochrome c-Caspases pathway has been linked to apoptosis [51], whereas the p53-Caspases-Cytochrome c cascade is involved in mitotic catastrophe [52]. There are a number of pathways that play a role in senescence, including the TNF (alpha) -PARP-JNK-Caspases pathway [53] and the MYC-INK4A-ARF-p53-p21 pathway [54]. It is believed that the PI3K-Akt-mTOR cascade plays a significant role in autophagy. There is still a lot we don't know about the cell death pathways that cause carcinogenesis in cancer cells and resistance to radiation treatment, even though most of these mechanisms are interconnected with radiation-induced cell death in cancer. Nevertheless, the exact process(es) that cause radiation to trigger various modes of cancer

cell death remain unclear. Our understanding of the several biochemical mechanisms that determine cell death following radiation exposure has been expanding at a rapid pace in recent years.

Radiation therapy's function in cancer treatment:

Killing cancer cells is the main objective of radiation treatment. Deoxyribonucleic acid (DNA) and other crucial molecules in biology are damaged to accomplish this. Interestingly, radiation interacting directly with these molecules only causes around one-third of the biological harm. Free radicals, formed when water is excited or ionised by radiation, are responsible for most of the damage since they are extremely reactive chemical entities that can destroy biological molecules. The second effect, which is also called indirect action, is responsible for around two-thirds of the biological harm that x-rays inflict. Notably, chemical sensitizers or protectors can alter indirect action, which is a crucial aspect.

Four biological mechanisms characterise cellular radiation sensitivity.

1. Fix it

DNA protein crosslinks, base changes, single-strand breaks, and double-strand breaks are the four main types of radiation-induced DNA damage. Because of how inefficiently they are healed, double-strand breaks are the most critical. The remaining ones, such as DNA protein cross-links, occur rarely or are easily repaired, such as nucleotide changes and single-strand breaks. Radiation carcinogenesis is a distinct but interconnected process, and all four pathways are capable of contributing to it.

2. Restocking

Some kinds of unharmed cells will eventually proliferate and replenish the population lost to irradiation. If this could happen more quickly in healthy tissues, like during repair, that would be great.

3. Shifting Funds

After irradiation, a greater number of cells will be in the radiation-resistant phase of the cell cycle than in the radiation-sensitive phase because different parts of the cell cycle are more radiation-resistant than others. Because of this, the effectiveness of following irradiation in destroying tumour cells would be diminished. It would be ideal if we could schedule the following treatments so that the tumour cells in the cohort would be in a sensitive phase again while the healthy cells would not.

Fourth, reoxygenation:

Radiation does not harm cells that are oxygen-starved, or hypoxia. The oxygen enhancement ratio (OER) relates the dosage required to have the same biological impact in oxygenated versus hypoxic environments. Both the cell cycle phase and the type of radiation (discussed below) play a role. Because oxygen diffuses only so far in tissues, cells in the tumor's core may be hypoxic and resistant to treatment compared to cells on the periphery. It is possible to make hypoxic areas more vulnerable to radiation by exposing them to oxygen and spreading the radiation out over multiple fractions, killing the tumor's outer parts. These processes can vary greatly in efficacy and relative relevance across various tissues. Irradiation has a greater effect on cells that divide quickly, such skin cells or intestinal lining, as opposed to those that do not divide as quickly, like neurons.

Endangering healthy tissues:

The potential for harm to healthy tissues is a key consideration when deciding how much dose to give the tumour, as we have already mentioned. There are two types of toxicity: acute and late. Tissues characterised by fast cell division are more likely to experience acute impacts. Radiation causes cell death during mitosis, which is why cells dividing quickly exhibit the highest rate of cell death. Skin and mucosal surfaces of the oropharynx, oesophagus, and rectum are a few examples. Mucositis is a common side effect of head and neck cancer treatments that usually worsens around the third or fourth week of treatment.

After that, it usually settles down because normal mucosal cell proliferation occurs in reaction to the cell death. Clinical personnel want to avoid discontinuing therapy due to severe reactions because doing so compromises tumour control and increases the total treatment time. In most cases, mucositis goes away once a few weeks of treatment is over. Irradiation has late consequences that manifest anywhere from six months to many years later. Among these complications are esophageal stricture, pulmonary fibrosis, and other organ damage. Acute symptoms are a direct predictor of future late consequences in certain circumstances (like esophagitis), while in other cases (like heart damage), there are no obvious acute symptoms.

Additional malignancies may develop as a result of radiation treatment. In contrast to the toxic consequences mentioned before, the intensity of cancer induction is thought of as a stochastic effect, and it grows worse with dosage. In other words, the severity is dosage-independent, even though the likelihood of occurrence grows with dose. Years following radiation therapy for paediatric Hodgkin's lymphoma or osteogenic sarcoma following radiation therapy for paediatric retinoblastoma are instances of radiation-induced secondary malignancies. Clinicians are highly unlikely to forego treatment for a patient due to fears about secondary cancers because the risks of the existing cancer outweigh those of a potential future cancer. When comparing treatment modalities that seem to have relatively similar tumour control outcomes, such as IMRT and proton therapies, the possibility of secondary malignancies is frequently brought up. This is why there is a strong emphasis on developing and refining treatment methods that minimise dosage to non-target tissues.

Treatment with Imaging-Guided Radiation:

In the past, patients would get themselves into the optimal posture for radiation therapy by lining up their tattoos with the lasers in the treatment chamber. Due to the skin's pliability, there are inherent daily uncertainties in patient positioning that can be somewhat substantial. The need to place the patient more precisely and consistently has arisen in tandem with the rise in accuracy of therapy administration. For a long time, x-ray imaging was the gold standard for patient positioning in the operating room. The process began with electronic portal imaging, which utilised the LINAC's radiation to generate images. There is less intrinsic contrast in these images compared to low energy x-rays since they are formed utilising high energy photons (MV), which are dominated by Compton interactions. Nonetheless, they suffice for patient alignment in the majority of instances. To get around this problem, newer LINAC systems attach kV x-ray tubes and detectors on arms to the gantry's side. This allows us to get better x-rays of the patient while they are in the treatment posture. Before beginning therapy, therapists can fine-tune the couch position by comparing daily x-ray images with treatment plan photos. The superior picture quality is a major benefit of this imaging method. One drawback is that it is still planar imaging, which works well for bone but frequently fails to show tumours and soft tissues. If the tumour is indeed linked to bone, then aligning the patient based on bone is a fair technique; nevertheless, there is still uncertainty regarding the tumor's ability to move relative to the boney landmarks. This is an improvement over using skin markers. This is the situation with prostate cancer and other malignancies of the chest and abdomen. A CT scan can be obtained by repositioning the kV x-ray tube and detector around the body, or by inserting radio-opaque markers within the tumour, both of which circumvent this problem. While the CT pictures produced by the second method are not of diagnostic imaging quality, they are generally more than enough for identifying and visualising soft tissue targets; this method is called cone-beam CT due to its geometric design.

Brachytherapy:

Brachytherapy is the placement of sealed radioactive sources in or on the tumor directly. It is characterized by a high dose to close to the source, which falls off with distance quickly (1/r2), giving low doses to adjacent or distant normal tissues.

Brachytherapy Application techniques

There are several standard ways in which brachytherapy sources can be used to treat tumors; the choice depends on the size and location of the tumor.

1. Interstitial brachytherapy.

This is the insertion of radio-active sources directly into the tissue. The sources may be permanently implanted, such as when I-125 seeds are placed in the prostate, or may be temporary, and removed after the required dose has been delivered. The advantage of a permanent implant is that it involves a one-time procedure. A temporary implant, however, may allow better control and adaptation of the source distribution and resultant dose distribution. With a typical temporary implant, one or several catheters are first inserted into the tissues. Dummy sources are then inserted into the catheters, and x-ray images are taken and used to localize the sources and calculate the dose distribution. The real radioactive sources are then inserted, and removed after the required dose has been delivered. For some treatments, the sources are inserted remotely using a computerized afterloading system.

2. Intracavitary brachytherapy.

This is the insertion of radio-active sources into a cavity in the body. The most common example is the treatment of uterine cancers. It is also possible to insert sources directly into the cavity created by a lumpectomy procedure for breast cancer. Intracavitary brachytherapy is always temporary, and, as with interstitial brachytherapy, the radioactive sources are handled either manually or remotely, depending on the strength of the sources.

3. External applicators.

When the tumor is close to the skin surface, radioactive sources can be inserted into tubes in specially fabricated molds 0.5 to 1.0 cm away from the skin surface. This may be preferable over external beam techniques for complicated irregular external surfaces.

Conclusion:

Cancer patients have benefited from radiation therapy for over a century. There are a lot of techniques available to tailor the radiation dose to maximise dose to the tumour while minimising dose to surrounding normal tissues; this is possible with today's very sophisticated treatment procedures. Nevertheless, there are still certain malignancies where we are battling to increase patient survival, despite the enormous scientific advancements of the last several decades. This highlights the critical need for further innovations, such as those involving nanotechnology.

Improvements in cancer patients' survival rates and quality of life have resulted from persistent attempts to develop novel radiation treatment methods and procedures. Reducing radiation-related side effects has risen to the top of the priority list in tandem with better cancer treatment results. Radiation technology advancements and the rise of mechanistic biology studies have led to better methods of dose fractionation and conformal radiation for protecting healthy cells and tissues. To further improve the radiation treatment's therapeutic ratio, radiation is also being administered in conjunction with molecular targeted therapy. There are still many unanswered questions, even though ionising radiation is still one of the best cancer treatments: 1. What factors cause cancer cells to choose a specific cell death pathway? The second question is: how does a cancer cell go from its repair programme to its destructive cell death programme? 3. Strategies to enhance the efficacy of radiation therapy when administered alongside other therapeutic modalities? 4. Is it feasible to mitigate the effects of radiation therapy on healthy tissues? Cancer treatment will continue to improve as we find answers to these and other problems, and as radiation therapy technology and practices evolve.

References:

1. Ringborg U, Bergqvist D, Brorsson B, Cavallin-Ståhl E, Ceberg J, Einhorn N, The Swedish Council on Technology Assessment in Health Care: systematic overview of radiotherapy for cancer

including a prospective survey of radiotherapy practice in Sweden 2001-summary and conclusions. Acta Oncol. 2003; 42: 357-365.

2. Delaney G, Jacob S, Featherstone C, Barton M: The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 2005; 104: 1129-1137.
3. Begg AC, Stewart FA, Vens C: Strategies to improve radiotherapy with targeted drugs. Nat Rev Cancer 2011; 11: 239-253.
4. Barnett GC, West CM, Dunning AM, Elliott RM, Coles CE, Pharoah PD, Burnet NG: Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat Rev Cancer 2009; 9: 134-142.
5. Bernier J, Hall EJ, Giaccia A: Radiation oncology: a century of achievements. Nature 2004; 4: 737-747.
6. Jackson SP, Bartek J: The DNA-damage response in human biology and disease. Nature 2009; 461: 1071-1078.
7. Bernier J, Hall EJ, Giaccia A: Radiation oncology: a century of achievements. Nature 2004; 4: 737-747.
8. Ellis F: Dose, time and fractionation: a clinical hypothesis. Clin Radiol. 1969; 20: 1-7. 16. International Commission on Radiation Units. Prescribing, recording and reporting photon beam therapy. Supplement to ICRU Report
9. Bethesda: International Commission on Radiation Units and Measurement. MD: ICRU; 1999.
10. Feng FY, Kim HM, Lyden TH, Haxer MJ, Feng M, Worden FP, Chepeha DB, Eisbruch A: Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. Int J Radiat Oncol Phys. 2007; 68: 1289-1298.
11. Wang-Chesebro A, Xia P, Coleman J, Akazawa C, Roach M 3rd: Intensity-modulated radiotherapy improves lymph node coverage and dose to critical structures compared to with three-dimensional conformal radiation therapy in clinically localized prostate cancer. Int J Radiat Oncol Phys. 2006; 66: 654-662.
12. Tipton K, Launders JH, Inamdar R, Miyamoto C, Schoelles K: Stereotactic body radiation therapy: scope of the literature. Ann Intern Med. 2011; 154: 737-745.
13. Lo SS, Moffatt-Bruce SD, Dawson LA, Schwarz RE, Teh BS, Mayr NA, Lu JJ, Grecula JC, Olencki TE, Timmerman RD: The role of local therapy in the management of lung and liver oligometastases. Nat Rev Clin Oncol. 2011; 8: 405-416.
14. Wu QJ, Wang Z, and Yin FF: The impact of respiratory motion and treatment technique on stereotactic body radiation therapy for liver cancer. Med Phys. 2008; 35: 1440-1451.
15. National radiotherapy implementation group report. Stereotactic body radiotherapy; Clinical review of the evidence for SBRT. UK: NRIG. 2010 30. Freeman DE, King CR: Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. Radiat Oncol. 2011; 6: 3.
16. Laramore GE: Role of particle radiotherapy in the management of head and neck cancer. Current Opin Oncol. 2009; 21: 224-231.
17. Schulz-Ertner D, Tsujii H: Particle radiation therapy using proton and heavier ion beams. J Clin Oncol. 2007; 25: 953-964.

18. Ma CM, Maughan RL: Within the next decade conventional cyclotrons for proton radiotherapy will become obsolete and replaced by far less expensive machines using compact laser systems for the acceleration of the protons. Med Phys. 2006; 33: 571-573.
19. Hall EJ: Cancer caused by x-rays-a random event? Lancet Oncol. 2007; 8: 369-370. 35. Baskar R: Emerging role of radiation induced bystander effects: Cell communications and carcinogenesis. Genome Integr. 2010; 1: 13.
20. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M: Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991; 21: 109-122.
21. Verheij M: Clinical biomarkers and imaging for radiotherapy-induced cell death. Cancer Metastasis Rev. 2008; 27: 471-480.
22. Dewey WC, Ling CC, Meyn RE: Radiation-induced apoptosis: relevance to radiotherapy. Int J Radiat Oncol Biol Phys. 1995; 33: 781-796.
23. Rupnow BA, Knox SJ: The role of radiation-induced apoptosis as a determinant of tumor responses to radiation therapy. Apoptosis 1999; 4: 115-143.
24. Cragg MS, Harris C, Strasser A, Scott CL: Unleashing the power of inhibitors of oncogenic kinases through BH3 mimetics. Nat Rev Cancer 2009; 9: 321-326.
25. Fogg VC, Lanning NJ, MacKeigan JP: Mitochondria in cancer: at the crossroads of life and death. Chin J Cancer 2011; 30: 526-539. 42. Eriksson D, Stigbrand T: Radiation-induced cell death mechanisms. Tumour Biol. 2010; 31: 363-372.
26. Sato N, Mizumoto K, Nakamura M, Ueno H, Minamishima YA, Farber JL, Tanaka M: A possible role for centrosome overduplication in radiation-induced cell death. Oncogene 2000; 19: 5281-5290.
27. Vakifahmetoglu H, Olsson M, Zhivotovsky B: Death through a tragedy: mitotic catastrophe. Cell Death Differ. 2008; 15: 1153-1162.
28. Jonathan EC, Bernhard EJ, McKenna WG: How does radiation kill cells? Curr Opin Chem Biol. 1999; 3: 77-83.
29. Hotchkiss RS, Strasser A, McDunn JE, Swanson PE: Cell death. N Engl J Med. 2009; 361: 1570-1583.
30. Roninson I: Tumor cell senescence in cancer treatment. Cancer Res. 2003; 63: 2705-2715.
31. Schmitt CA: Cellular senescence and cancer treatment. Biochim Biophys Acta. 2007; 1775: 5-20.
32. Ito H, Daido S, Kanzawa T, Kondo S, Kondo Y: Radiation-induced autophagy is associated with LC3 and its inhibition sensitizes malignant glioma cells. Int J Oncol. 2005; 26: 1401-1410.
33. Kuwahara Y, Oikawa T, Ochiai Y, Roudkenar MH, Fukumoto M, Shimura T, Ohtake Y, Ohkubo Y, Mori S, Uchiyama Y, Fukumoto M: Enhancement of autophagy is a potential modality for tumors refractory to radiotherapy. Cell Death Dis. 2011; 2: e177.
34. American Association of Physicists in Medicine, D. W. O. Rogers, and J. E. Cygler. 2009. Clinical dosimetry measurements in radiotherapy. Proceedings of the American Association of Physicists in Medicine Summer School, Colorado College, Colorado Springs, CO, June 21–25, 2009. Madison, WI: Medical Physics Pub.
35. Bentzen, S. M., L. S. Constine, J. O. Deasy et al. 2010. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): An introduction to the

scientific issues. International Journal of Radiation Oncology Biology Physics 76:S3–S9.

36. Cody, D., and O. Mawlawi. 2008. The Physics and Applications of PET/CT Imaging. Madison, WI: Medical Physics Publ. Corp. Cox, J. D., and K. K. Ang. 2003. Radiation Oncology: Rationale, Technique, Results. 8th ed. St. Louis, MO: Mosby.
37. Ezzell, G. A., J. M. Galvin, D. Low et al. 2003. Guidance document on delivery, treatment planning, and clinical implementation of IMRT: Report of the IMRT subcommittee of the AAPM radiation therapy committee. Medical Physics 30:2089–2115.
38. Hall, E. J. 2000. Radiobiology for the Radiologist. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins.
39. Hall, E. J., and A. J. Giaccia. 2006. Radiobiology for the Radiologist. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins.
40. Hartford, A. C., M. G. Palisca, T. J. Eichler et al. 2009. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) Practice Guidelines for intensity-modulated radiation therapy (IMRT). International Journal of Radiation Oncology Biology Physics. 73:9–14.
41. Hendee, W. R., G. S. Ibbott, and H. G. Hendee. 2005. Radiation Therapy Physics. 3rd ed. Hoboken, NJ: Wiley. International Commission on Radiation Units and Measurements. 1997. Dose and Volume Specification for Reporting Interstitial Therapy.
42. Bethesda, MD: International Commission on Radiation Units and Measurements. International Commission on Radiation Units and Measurements. 1998. Clinical Proton Dosimetry.
43. Johns, H. E., and J. R. Cunningham. 1983. The Physics of Radiology. 4th ed. Springfield, IL: Charles C. Thomas.
44. Karzmark, C. J., and R. J. Morton. 1998. A Primer on Theory and Operation of Linear Accelerators in Radiation Therapy. 2nd ed. Madison, WI: Medical Physics Pub.
45. Khan, F. M., AAPM Radiation Therapy Committee. Task Group No. 25. 1991. Clinical Electron-Beam Dosimetry: Report of Task Group No. 25, Radiation Therapy Committee, AAPM. New York: Published for the American Association of Physicists in Medicine by the American Institute of Physics.
46. Khan, F. M. 2007. Treatment Planning in Radiation Oncology. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins.
47. Marks, L. B., S. M. Bentzen, J. O. Deasy, F.-M. Kong, J. D. Bradley, I. S. Vogelius et al. 2010. Radiation dose–volume effects in the lung. International Journal of Radiation Oncology*Biology*Physics 76(3, Supplement):S70–S76.
48. Metcalfe, P., T. Kron, and P. Hoban. 2007. The Physics of Radiotherapy X-rays and Electrons. Madison, WI: Medical Physics Pub.
49. Otto, K. 2008. Volumetric modulated arc therapy: IMRT in a single gantry arc. Medical Physics 35:310–317. #
50. Partridge, M., Mi. Ramos, A. Sardaro, and M. Brada. 2011. Dose escalation for non-small cell lung cancer: Analysis and modelling of published literature. Radiotherapy and Oncology 99(1):6–11.
51. Podgoršak, E. B., International Atomic Energy Agency. 2005. Radiation Oncology Physics: A Handbook for Teachers and Students. Vienna: International Atomic Energy Agency.
52. Thomadsen, B., M. J. Rivard, W. M. Butler et al. 2005. Brachytherapy Physics. 2nd ed. Madison, WI: Published for

American Association of Physicists in Medicine by Medical Physics Pub.

53. Washington, C. M., and D. T. Leaver. 2004. Principles and Practice of Radiation Therapy. 3rd ed. St. Louis, MO: Mosby Elsevier.

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