Translational Medical Physics in Cancer Treatment: Mechanisms of Radiation Science Therapeutics

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The Basics of Radiotherapy

The advent of modern radiotherapy is a cross disciplinary development between the fields of biomedical engineering, medicine, and the basic sciences which has provided the scientific community with an innovative and continually developing arsenal in the fight against cancer. At the forefront of this battle is the utilization of radiotherapy to treat cancers of different morphological and embryological origins. According to the Royal College of Radiologists, surgery accounts for 49% of successful tumor therapy, while radiotherapy weighs in at an impressive and ever-growing 40%; clearly, the continued research and economic investment in radiotherapy is worthwhile, given the technological complexity of medical physics [1]. The distinct types of radiotherapy treatments converge on a few fundamental goals: killing cancer cells, halting the possible metastasis of cancer cells, sparing healthy tissue from undesirable radioactive damage and palliation via pain relief and tumor regression. The particular type of radiation therapy prescribed by a radiation oncologist depends upon the tumor type, grade and stage, and its location in the body relative to surrounding healthy tissue. While much of the biology specific to radiation response has been described, there is still a considerable amount of research needed to find optimal radiotherapy in each specific case.

As this dynamic field of medicine continues to unravel its healing potential, the oncologic community learns which distinct types of radiotherapy treatments are most efficacious for each different cancer type [2]. Further, various clinicopathologic factors will dictate whether a patient will receive treatment prior, during or after surgery, or whether both surgery and radiotherapy is necessary in their personalized cancer treatment. Further, the type of radiation is determined specifically for each patient and tumor. When a patient is given pre-operative radiation therapy, the goal is usually to shrink a tumor so that it can subsequently be removed by surgery. Intraoperative radiation therapy (IORT) is given during the surgical procedure and may fall under two distinct categories: external beam radiation therapy (utilizing photons or electrons) or brachytherapy. Which modality of treatment is best under the given circumstances, as well as how that treatment is delivered to the patient, is something which science and medicine continue to decipher.

In order to demonstrate the fundamental differences between the utilization of different treatments, both in regards to biochemical and molecular effects and clinical modalities, it is essential to compare and contrast the methods of delivery in radiotherapy. Once the modes of clinical delivery are clearly outlined, the efficacy of these therapies can be understood more thoroughly in regards to the subatomic particles being utilized in each modality. To this end, we will review the repertoire of radiation modalities utilized today and the differences amongst them; subsequently, the differences between types of particulate and sub-atomic particles utilized in each modality is appropriately discussed in order to appreciate and comprehend the logic behind the advantages and disadvantages of each modality utilized in clinical radiation therapy for the treatment of an array of cancers.

Key Differences between the Chief Modalities for the Delivery of Radiation Therapy

Differences in intra-operative radiotherapy, brachytherapy and systemic radiation therapy

Intraoperative radiotherapy (IORT) is a technique in which a high, single-fraction radiation dose is delivered during a surgical procedure to macroscopic tumors, or immediately after resection to the operative bed, with minimum exposure to surrounding tissue. IORT can be done with a number of modalities, including utilization of an electron beam or high dose rate brachytherapy, also known as HDR- IORT. In a meta-analysis of 29 studies examining the efficacy of IORT in colorectal cancer patients, Mirnezami et al. report a significant effect with improved local control, disease free survival and overall survival in the 3003 patients (HR 0.33; 95% CI=0.2–0.54; p=0.001) [3]. Brachytherapy is the delivery of radiation from sources which are placed within or against the body, either within or adjacent to the tumor. Radioactive isotopes are commonly sealed in pellets and placed within the target organ via delivery devices such as catheters or needles. The source of radioactive isotopes can be placed in small sealed vials and is most frequently utilized to treat tumors of the head and neck, prostate, cervix and breast [4]. In contrast with unsealed source radiotherapy, in which the radioisotope is injected into the body, brachytherapy has the advantage of direct input into the tumor site. In systemic radiation therapy, a patient swallows or receives an injection of a radioactive substance, such as radioactive iodine or a radioactive substance bound to a monoclonal antibody. A monoclonal antibody assists targeting the radioactive substance. The antibody joined to the radioactive substance travels through the blood, where it eventually can encounter its target and bind, allowing for an opportunity to deliver its radiation dose while it naturally decays at a short distance from the target (the tumor cells) by damaging the DNA structure. A key feature of brachytherapy is its ability to localize treatment and minimize damage done via radiation to healthy tissue as the dose fall-off is very sharp.

External-beam radiotherapy: intensity modulated radiotherapy and image guided radiotherapy

External Beam Radiotherapy (EBRT), the most common form
of radiation therapy, directs the planned radiation dose at the target from outside of the body. External-beam radiation therapy can be delivered by a number of different methods, most commonly utilizing photon and proton beams. Proton beams (and other charged particulate radiations) differ from photon beams in that they deposit most of their energy at the end of their path—the Bragg peak—while photons deposit their energy in small packets all along their trajectory through the body [5]. A painless and relatively quick procedure, patients typically receive EBRT in daily treatment sessions over the course of several weeks, 5 days a week, depending on the desired dose to be obtained. Modifications of timing, intensity and duration of therapy for individual tumour type remain an area of scientific enquiry. Intensity modulated radiation therapy (IMRT) is a method of delivery of EBRT in which each individual beam is modified to account for the shape of the tumour. This is typically accomplished by using radiation beam-shaping devices, called multi-leaf collimators (MLCs), to deliver a single dynamic dose of radiation. MLCs can either be stationary or mobile during treatment, thus allowing the intensity of the radiation beams to change during treatment sessions and making patient throughput less onerous. The advantage of IMRT in comparison to other forms of treatment is its ability to modulate doses and consequently allow different areas of a tumor to receive various doses of radiation as well as its ability to spare normal tissue. IMRT has been successfully used to treat tumors when the target area is readily identifiable at the initiation of daily treatments and the desired dose for optimum tumor control is significantly higher than the acceptable dose limits for adjacent normal tissue [6].

Molecular Genetic Damage: Comparing Atomic Particles Characteristics

Ionizing radiation interaction with DNA

Tsujii and Kamada report that ion beams such as protons and carbon ions, in comparison with photons, can provide beneficial dose distributions [7,8]. Further, being that carbon ions are heavier than protons, a larger relative biological effectiveness exists for carbon ions, which thereby leads to a higher probability of tumor control with the lesser volume of the surrounding normal tissues irradiated [8]. Photons and fast neutrons are characterized by an exponential absorption of dose with depth, while ion beams demonstrate an increase in energy deposition with penetration depth up to the sharp maximum at the end of their range. The rate at which a particle beam loses its energy as it penetrates matter, or human tissue, increases with the mass of the particles. Ionization will result when the energy transferred to the bound electrons, either by a photon or by a collision, exceeds the binding energy. This is known as linear energy transfer—LET. Low LET radiations include photons, electrons and protons, while neutrons and carbon ions are examples of high LET radiations.

Upon the incidence of ionizing radiation with DNA, a variety of molecular lesions can occur which can have potentially fatal end results. Radiation has the potential to induce single stranded breaks (by far the most common), double stranded breaks, complex mixtures of double stranded breaks, and DNA protein crosslinks. In general, the Relative Biological Effectiveness of varying radiotherapeutic methods depends on the quality of radiation, the dose and dose-rate, as well as the status of the biological system being targeted [9]. The latter category may include important factors such as cell type, genetics, the stage of the cell cycle, and the percentage of oxygen at which the system is currently under [10]. Photons are characteristic of a random energy distribution through the targeted matter [11]. However, photon beams generate relatively low ionization levels and therefore many photons are required to achieve relevant therapeutic goals. Particle beams, such as heavy ion beams, differ in their spatial distribution of energy. The track structure produces a radial dose distribution around the ion path, which follows 2 steps: the emission of electrons by Coulomb interaction and scatter of the emitted electrons [12]. In low LET radiation, indirect DNA damage is found to be greater, whereas in high LET radiation there are greater direct hits [13].

Comparing various beam types in radiotherapy

Hall and Wuu addresses a comparative advantage of using proton therapy and ion beams: the Bragg peak [14]. This feature allows high doses to be targeted within the tumor with either no dose or very low dose to more distal normal structures. The likelihood of causing radiation-induced second cancers later in life is also reduced, which illustrates the promising effects that protons and ion beams may have in the treatment of pediatric cancers [15]. Furthermore, it is interesting to note the advantage of ion therapy reported by Brenner et al. in which he reports that the overall RBE of ion beams is greater than conventional X-ray beams [16]. Therefore, relative to X-rays, less radiation dose is required to produce a given biological effect when using ion beams in radiation therapy. Theoretically, use of protons should reduce the exposure of normal tissue to radiation, possibly allowing the delivery of higher doses of radiation to a tumor.

Possible Adverse Advents Involved in Radiotherapy

In the early 1960s Hall et al. state that the dose-response relationship for radiation induced malignancies would be bell-shaped, thereby indicating that the incidences would rise at low doses but fall at high doses. This dynamic of radiation induced damage could be explained by two mechanisms: 1) a dose-related increase in the proportion of normal cells that are transformed to a malignant state and 2) a dose-related decrease in the probability that transformed cells may survive the radiation exposure. The balance between cell killing and cell transformation leads to the overall bell-shaped outcome of the dose relationship for radiation carcinogenesis at high doses [10]. In an evaluation of 1,612 patients with acute lymphoblastic leukaemia who were irradiated, St. Jude Children’s Research Hospital reported an excess of high-grade gliomas and meningeomas during the first decade of follow up. An increased risk of low-grade brain tumors was also observed at later follow-up intervals. These studies suggest that the risk of brain tumors increased with increasing radiation dose. As a consequence of these studies, prophylactic cranial radiotherapy in children with leukaemia has been largely replaced by intrathecal mexitrexate [10].

The quantity used to measure the amount of ionizing radiation is the absorbed dose. This is defined as the energy absorbed per unit mass, quantified as joules per kilogram, or Gray (J/kg=1 Gy). Hall et al. explain that if the body is uniformly irradiated, the probability of the occurrence of stochastic effects, cancer and hereditable effects is assumed to be proportional to the equivalent dose. It is well established that various organ tissues differ substantially in their sensitivity to radiation induced stochastic effects [17]. For example, it is difficult to produce heritable effects by irradiation of the head or hands, yet the thyroid and breast are particularly susceptible to radiation-induced cancer. Enhanced sensitivity of cancer predisposed genotypes to cancers induced by ionizing radiation is heavily debated. Chakraborty and Sankaranarayanan report that individuals genetically predisposed to cancer may be more sensitive to cancers induced by ionizing radiation than those who are not so predisposed [18]. In a
meta-analysis of 127 articles, Marjikje et al. reports an increased risk of breast cancer among high-risk women due to low-dose radiation exposure (OR=1.3, 95% CI: 0.9–1.8). Exposure before age 20 (OR=2.0, 95% CI: 1.3–3.1) or a mean of ≥ 5 exposures (OR=1.8, 95% CI: 1.1–3.0) was significantly associated with a higher radiation-induced breast cancer risk [19]. This significantly illustrates that when women with familial or genetic aggregation of breast cancer are treated with low-dose radiation a careful approach is needed, by means of reducing repeated exposure, avoidance of exposure at a younger age and using non-ionising screening techniques. Radiation sensitivity may also be attributed to specific genetic mutations. Diseases of radiation sensitivity include ataxia telangiectasia (AT) and Nijmegen break-gene mutations. Sharif et al. [20] report second primary tumors in neurofibromatosis 1 (NF-1) patients treated for optic gliomas after radiotherapy. Optic pathway gliomas are the most common CNS tumor in NF-1 patients, and the long-term risk of second tumors in NF1-related optic pathway gliomas after radiotherapy was evaluated. In this study, 50% of the 18 patients who received radiotherapy for their optic pathway gliomas developed second tumors in 308 person-years of follow-up after radiotherapy. In the same study, though, 20% of 40 patients who were not treated with radiotherapy developed tumors in 721 person-years of follow up after the diagnoses of their optic pathway gliomas. The conclusion of this study was that there is a significant increase of risk for secondary nervous system tumors in NF-1 patients who receive radiotherapy for their optic pathway gliomas. Therefore, radiotherapy should only be used if absolutely essential [20].

Conclusion

Radiation therapy remains a very effective tool in the clinical management and cure of cancer and new techniques of radiation delivery continue to be developed. Innovative research continues to illustrate the efficacy of certain subatomic particles in the treatment of cancer, as well as the effectiveness of specific treatments for certain types of cancer. Thus, although it is clear that each technology holds its advantages in comparison to its partner, these identified pros and cons types of treatment bring us one step closer to finding a personalized cure for each particular type of cancer.

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References


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