

TITLE: The Principles of Radiation Oncology

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Introduction

Radiation therapy either used alone or in combination with surgery and/or chemotherapeutic modalities has become an important aspect in the treatment of head and neck cancer. A basic understanding of the principles of radiotherapy will benefit the otolaryngologist in planning treatment strategies for these patients. The following discussion outlines the basic principles of radiation oncology and is intended to provide a clear understanding of the biologic basis for the use of ionizing radiation in treating head and neck cancer.

Radiation Physics

The basis of radiation therapy is the interaction of ionizing particles (x-rays, gamma rays or electrons) with tissues at the molecular level. This interaction depends on the energy created by the production of secondary charged particles, usually electrons, which can break chemical bonds and inflict cellular injury. Radiation therapy is delivered by external beam, an interstitial implant, or combination of the two. External beam radiation therapy entails generation of energy particles at some distance from the patient. Interstitial implants, or brachytherapy, entails placement of radioactive sources near or within the tumor. Radiant energy is deposited in biologic material in a discrete yet random fashion, and the biologic effects occur as a result of the transfer of energy to atoms or molecules within the cell.

External Beam Irradiation

Dual-energy linear accelerators allow for the generation of either low-energy megavoltage x-rays (4-6 MeV), high-energy megavoltage x-rays (15-20 MeV) or electrons. Most patients are treated with x-rays or gamma rays (photons) because of the skin-sparing properties, penetration and beam uniformity. Due to the typical location of head and neck cancers (7 to 8 cm deep) and regional lymph nodes (superficial), 4 to 6 MeV x-rays or cobalt 60 gamma rays are typically used. Additional treatment (a boost) with 15 to 20 MeV x-rays can be used for the base of tongue or nasopharynx. Electron beams are useful for managing superficial

lesions, because of their finite range and deep tissue sparing properties.

Brachytherapy

This is a technique in which radioactive sources are placed directly into the tumor and surrounding tissues (interstitial implants), within body cavities (intracavitary therapy), or onto epithelial surfaces (surface molds). The advantages of this therapy over external beam are that a greater dose can be delivered to the tumor at a continuously low dose rate. This allows for a theoretical advantage in the treatment of hypoxic or slowly proliferating tumors and potentially, shorter treatment times. The tumor must be accessible and well demarcated. It should not be the only treatment modality for tumors with a high risk of regional lymph node metastasis.

Radiobiology

The energy of therapeutic radiation is high enough to eject an electron from a target molecule, thus, the term ionizing irradiation. Ionizing energy is distributed randomly within the cell so that the x-rays hit a wide array of molecules. A DNA double strand break is generally believed to be responsible for cell death, which is determined by cells that are no longer able to undergo cell division. The injury responsible for cell death can occur directly or indirectly, via free radicals (molecules with an unpaired electron, e.g., $\text{DNA} \rightarrow \text{DNA}\bullet$). Free radicals are highly reactive and can either be reduced by cellular mechanisms (repaired DNA) or stabilized by oxygen (permanent DNA-OO \bullet damage). Inadequate repair of DNA lesions, either nucleotide base damage or single/double strand breaks, can lead to cell death or mutation.

Random Cell Death

The deposition of ionizing energy is a random event as is the resultant radiochemical injury. Therefore, any given cell within a tumor has an equal chance of being hit by a given dose so that the same proportion of cells within the tumor is damaged per dose. In other words, the same dose of radiation will reduce the cell population from 100 cells to 10 cells as it will 10 billion cells to 1 billion cells. This means that a more radiation is needed to eradicate larger tumors. Furthermore, a tumor is no longer palpable when it is reduced to 10^5 cells, so clinical response rates do not relate to effectiveness of the radiation dose. Finally, this random nature of cell death applies to normal tissue as well as tumor cells. A therapeutic advantage may be gained by one of four hypothetical mechanisms: repair of damage, reoxygenation of the tumor, redistribution within the cell cycle, and repopulation of tumor cells. These mechanisms are known as the classical four R's of radiation biology.

Repair of sublethal injury

When a secondary electron passes through matter, a cell may be exposed to either dense or sparse ionization. It is thought that cells are more likely to repair damage inflicted by sparse ionization within the field of radiation. This sublethal injury can be repaired if no further hits are sustained. Therefore, a greater total dose is needed to produce a biologic effect when given in several fractions as opposed to a single fraction. The greater the number of fractions, the greater is the opportunity for repair between dose fractions. However, the same biologic effect requires a greater total dose. In most tissues, sublethal injury is repaired within 3 hours, but up to 24

hours may be necessary for some tissues. This concept explains why radiation therapy is fractionated. It allows repair of injured normal tissue, providing an overall therapeutic advantage over tumor cells. In contrast, this also may explain the radioresistance of certain malignant cell types, which have a remarkable ability to repair sublethal injury (i.e., melanoma).

Reoxygenation of Tumors

Oxygen, as discussed previously, is important for its effects on stabilization of free radicals produced by ionizing radiation. Hypoxic cells generally require an increased dose of radiation for lethal effect. Hypoxic regions within cancerous tissue can occur secondary to temporary constriction or collapse of capillaries or when tumors outgrow their blood supply. During radiation treatment hypoxic areas within the tumor decrease as the size of the tumor diminishes, compressed blood vessels open, and hypoxic cells are brought closer to capillaries. Reoxygenation is another reason why radiation is given in fractionated doses. Tumor hypoxia is another potential cause of radioresistance. Recently, hypoxic cell radiosensitizers and agents selectively toxic to hypoxic cells have been developed for clinical use with concurrent radiotherapy.

Redistribution within the Cell Cycle

Each individual cell's position in the cell cycle influences its radiosensitivity. Cells undergoing DNA synthesis, the S phase, are much more radioresistant than are cells in other phases of the cell cycle. There is increasing evidence that the ability of a cell to be delayed in the G₂ phase of the cell cycle corresponds to its ability to survive irradiation. Studies of the RAD9 gene mutation producing radiosensitivity in yeast have shown these cells do not undergo a delay in G₂ following irradiation. In addition, radioresistant rat embryo cells transformed with oncogenes, H-ras and c-myc, showed a G₂ delay and more radioresistance than control cells. When radiation treatment is fractionated, surviving cells redistribute into more sensitive phases of the cell cycle, making them more susceptible to subsequent fractions. The sensitizing effect of redistribution tends to offset sublethal injury repair. Furthermore, rapid cycling cells redistribute better between fractions than slowly cycling cells. Skin and mucosa cells cycle rapidly and are responsible for acute reactions to irradiation. Connective tissue, brain and blood vessels cycle more slowly and are responsible for late effects. It is the tissues responsible for late complications that are spared more by fractionation of treatment.

Repopulation

As cells are lost to radiation injury and death within a given population of normal or tumor cells, the surviving cells respond by increased regeneration or repopulation. Repopulation is a greater problem with rapidly proliferating tumors than slower growing neoplasms. Regeneration is therefore one of the determinants for planning the length and timing of a course of therapy, and a balance between adequate tumor control and sufficient sparing of acutely reacting normal tissues to allow recuperation must be reached. Accelerated treatment schedules with twice-daily fractionation and combined accelerated-hyperfractionated schedules have been developed to diminish the opportunity for tumor repopulation. It is likewise, the reason not to delay treatment after incomplete resection and to avoid protracted courses of therapy or split-course treatment schedules.

Dose-Response Relations

The probability of controlling cancerous lesions with radiotherapy depends on the size of the tumor and the dose of radiation given. The dose-response relation for small, well-vascularized neoplasms is steep, because they are relatively homogeneous, are well oxygenated and have approximately the same number of cells. Bulky tumors, however, are more heterogeneous with considerable variability in number of cells and oxygenation. Therefore, the dose-response curve is much shallower. The dose-response relation for normal tissue injury is the limiting factor in the amount of irradiation that can be given. As the size of the tumor increases, and the dose needed for local control likewise increases, the risk of injury to normal tissue becomes greater.

Fractionation Schedules

Conventional fractionation schedules are typically in increments of 1.8 to 2.0 Gy given five times per week for 6 to 8 weeks. Altered fractionation schedules have been developed in an attempt to optimize treatment results under various clinical circumstances. In essence, the objective of altered fractionation is to improve the therapeutic ratio through an alteration of time, dose, and/or fractionation based on the differential response of tumors and normal tissues to these altered schedules. Accelerated fractionation involves two or more dose fractions of the conventional size per day in an attempt to shorten overall treatment time. In theory, this may minimize tumor repopulation during treatment and, therefore, increase the probability of tumor control for the same total dose. Hyperfractionation involves the administration of two or more smaller dose fractions per day for a conventional or slightly longer treatment time. Theoretically, with hyperfractionation it is possible to increase the total dose, thereby increasing the probability of tumor control without increasing late complications.

Treatment

The treatment strategy for an individual patient with head and neck cancer is based on the size and location of the primary lesion, the presence or absence and extent of regional or distant metastatic disease, and the general condition of the patient. Early-stage head and neck cancer usually is effectively managed with either surgery or radiation therapy alone. The choice between these two modalities of treatment is often determined by the functional deficit that would result from the proposed treatment. Larger cancers are generally managed with a combination of surgery and radiation. Radiation therapy alone is sometimes attempted, and in this case, surgery is reserved for salvage of tumor recurrence. Surgical salvage of radiation failures is generally more effective than radiation salvage of surgical failures.

A course of radiotherapy is usually delivered using a shrinking field technique. This is based on the concept that tumor cell killing by radiation is an exponential function of dose and that the dose required for a particular tumor control probability is proportional to the logarithm of the number of viable cells in the tumor. For example, the initial tumor dose of 45 to 50 Gy usually is delivered in 4.5 to 5 weeks through large portals that cover the clinically involved region and areas of possible regional lymph node metastasis. The field is then reduced to encompass only gross tumor with a small margin (boost fields) and an additional 15 to 25 Gy is delivered over the next 1.5 to 2.5 weeks to bring the total dose to 60 to 75 Gy in 6 to 7.5 weeks.

With massive tumors, a second field reduction at 60 to 65 Gy is performed. An additional 10 to 15 Gy is given through small fields for a total dose of 70 to 75 Gy in 7 to 8 weeks. The spinal cord should not receive more than 45 Gy to avoid the risk of radiation myelitis.

When used appropriately, combining surgery and radiotherapy complement one another very well. Surgery is ideal for removal of gross tumor, and most radiation failures are the result of an inability to control bulky masses. Radiotherapy is very effective in controlling microscopic disease, and often surgical failures occur as a result of leaving subclinical tumor extensions, or microscopic disease, behind. Intuitively, combining the two modalities effectively counteracts the limitations of the other. Radiation can be administered either pre- or post-operatively.

Preoperative radiotherapy may decrease tumor bulk to facilitate dissection. Also, microscopic disease may be more effectively controlled prior to disturbing its blood supply. Tumor cell seed may be diminished, and it may be possible to use smaller treatment portals preoperatively. A typical preoperative dose is 45 Gy in 4.5 weeks. This dose is sufficient to eradicate subclinical disease among 85% to 90% of patients.

Postoperative radiotherapy, on the other hand, enables more accurate surgical staging. The dissection is much less difficult in tissues that have not been previously irradiated, and surgical complications are often reduced because healing is generally better. Finally, a larger dose of radiation may be given postoperatively than preoperatively. The typical postoperative dose is 60 to 65 Gy over 6 to 7 weeks. Postoperative radiotherapy markedly reduces the risk of recurrence in the surgical field, however the results are poorer if delayed more than 6 weeks.

Complications

Acute Tissue Reactions (Acute Toxicity) – The time course for developing acute radiation reactions depends on the cycling time of the cells affected. Mucosal reactions begin to appear in the second week of irradiation. Skin reactions appear in the fifth week. Acute effects generally subside several weeks after completion of treatment and are not a serious problem.

The Radiation Therapy Oncology Group (RTOG) considers acute toxicities to occur within 90 days of the commencement of radiotherapy. This definition reflects the observations from conventional fractionation schedules of the 1980s when this definition was created. Epithelial surfaces generally heal within 20 to 40 days after completion of treatment. With the development of aggressive radiation and chemoradiation schedules in recent years, prolonged acute effects have been noted which can last beyond the 90 day window.

Mucosal toxicity, or mucositis, is usually the intensity-limiting side effect of aggressive radiation therapy schedules. Accelerated fractionation trials and concurrent chemoradiation programs are associated with progressively higher rates of mucosal toxicity. The conservative approach to conventional fractionation schedules emphasized low rates of severe acute reactions and recognition that the maximum tolerated total dose should be limited by late tissue injury, not acute toxicities.

Late Tissue Reactions (Late Toxicity) – Late effects from radiotherapy are a concern because the injury is often permanent. These effects occur in tissues composed of functional

parenchymal cells with very low cell turnover rate that retain the flexibility to regain reproductive function in the event of tissue loss. Most late effects in the head and neck develop within the first 3 years of treatment and a few appear or progress after 3 years. The late effects of radiation for head and neck cancer include xerostomia, damage to teeth, fibrosis, soft-tissue necrosis, bone necrosis, cartilage necrosis, and damage to the eye, ear, and central nervous system. While chronic xerostomia is perhaps the best known late complication, many patients also experience chronic fibrosis, edema, trismus, dysphagia, or other organ dysfunction.

Xerostomia occurs from injury to the serous cells within the salivary glands, and usually occurs with doses larger than 35 Gy in 3.5 weeks. Once lost, this function may or may not return, but no more than partial recovery is typically expected. Dental caries often results from the decrease in salivary flow and unlike other late effects of radiation, teeth both inside and outside the radiation fields can be affected.

Osteoradionecrosis results from overlying soft tissue necrosis. Cartilage necrosis can occur as well. Soft tissue necrosis manifests as mucosal ulceration and is thought to be caused by damage to vascular connective tissue.

Severe skin damage is relatively uncommon due to the skin sparing properties of modern radiation therapy equipment. A serious problem, and the principle dose-limiting factor of radiation, is fibrosis of the subcutaneous tissues and muscle. In the most severe cases, the tissue can develop a woody texture and become fixed. Large daily fractions and treatment of massive neck disease increase the risk of fibrosis.

The potential ocular complications may include cataracts, injury to the optic nerve, retinopathy, or damage of the lacrimal gland. Otologic complications of serous otitis media or even sensorineural hearing loss may occur with treatment of the nasopharynx and ear, respectively.

Central nervous system complications of radiotherapy are of special concern with regard to radiotherapy, because the results are devastating to patients. Radiation induced myelopathy can occur with doses as low as 30 Gy in 25 fractions, and is characterized by electric shock sensations triggered by flexing the cervical spine (Lhermitte sign). Transverse myelitis is a rare complication after doses of 50 to 60 Gy. Somnolence syndrome may appear months after therapy and is characterized by lethargy, nausea, headache, cranial nerve palsy, or ataxia. This is usually a transient and self-limiting condition. Brain necrosis is a permanent injury that can develop after doses of 65 to 70 Gy.

Conclusions

Radiation therapy plays a key role in the treatment of head and neck cancer as it is often used as in a primary or combined fashion. The basic concepts of radiation physics and radiobiology help to explain the rationale for radiation treatment schedules and the reasons for associated complications. An understanding of these fundamentals is essential to the otolaryngologist in order to adequately counsel head and neck cancer patients regarding their treatment options and the possibility of serious side effects after radiation therapy.

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