Radiation Therapy

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Radiotherapy has had a role in malignancies for the last century. X-rays were discovered by Von Roentgen in 1895 and were used diagnostically. The element radium was isolated by Marie and Pierre Curie in 1898. The first therapeutic report of a patient cures by radiation therapy was in 1899.

However it has a diminishing role in childhood malignancies due to more effective chemotherapy regimens and the recognition of late effects of radiation treatment. Children will often be assessed on an individual level regarding the need of radiotherapy. However it is still required for around 20% of children and young people with cancer.

Focus in radiation therapy (XRT) has been on methods of delivery that will minimize injury to normal tissues, to try to avoid long-term negative sequalae.

9.1 Principles of treatment

Radiotherapy causes damage to cells in a localised area. Ionising radiation both causes and treats cancer. Damage is caused by breaking strands of DNA; either double or single strands. This inhibits cell division. It may harm normal cells in the area they pass through or in the area around tumor.

Radiation treatment has three main roles in the treatment of childhood and young person's cancer:

- Radical: Treatment with curative intent
- Adjuvant: "Added on" treatment
- Palliative: Treatment aimed at symptom control.

Radiation is frequently used as part of a bone marrow ablative regimen. At times radiation may be used to ameliorate side effects from tumors that are threaten life or organ function; to quickly reduce the size of a mass that is impinging on the airway, or to relieve pressure on the spinal cord to decrease or prevent paralysis.

Palliative radiotherapy is given to relieve pain in progressive or metastatic disease. It provides shrinkage of tumor to relieve pain and/or obstructions interfering with quality of life. The dose is monitored to ensure minimal toxicities.

9.2 Description of treatment

All radiation emits radiant energy; either in waves and particle form.

- Electrons are electromagnetic and produced from a linear accelerator. They can provide treatment to superficial tumors and have increased absorption to bone. (X-rays are electromagnetic radiation that is produced extranuclearly; electrons are accelerated to high energy and then stopped abruptly at a tungsten target (Farah and Weichselbaum 1994)).
- Gamma rays are electromagnetic radiation produced intranuclearly from a radioactive source. They provide local and wide-field radiation, and are skin sparing. Gamma rays require lead or concrete to absorb them.
- Protons are high energy atoms, emitted from a machine, for the treatment of tumours needing specific dose localization. They are delivered by stereotaxis (a form of radiation that delivers the beam in an extremely precise manner).

9.2.1 Cell radiosensitivity

Factors that contribute to cell radiosensitivity include:

- Phase of cell cycle that cell is in: Studies have shown that cells are most radiosensitive in the M and G2 phases and most resistant in late S phase (Farah and Weichselbaum 1994). Between dose fractions, cells may move through the cell cycle to more sensitive phases. This process is called "reassortment". This allows for a greater cell kill.
- Rate of division: Rapidly dividing cells are more likely to be in the dividing phase of the cell cycle; therefore they are more radiosensitive.
- Oxygenation: Hypoxic cells tend to be radioresistant and only a small quantity of oxygen is required for radiosensitisation. During the course of treatment, oxygenated cells are killed, tumours become smaller, and hypoxic cells move to the well-oxygenated compartments (Farah and Weichselbaum 1994). This is termed reoxygenation. A patient's haemoglobin should be maintained at a minimum of 10 gms/dl.
- Degree of differentiation of cell type: Poorly differentiated cells are more radiosensitive.
- Use of radiosensitizers: Certain chemotherapeutic agents have been known to increase tumor cells' sensitivity to radiation and are often used in combination with radiation to optimize cell kill (Tarbell and Kooy, 2002). These agents include dactinomycin, doxorubicin, etoposide and methotrexate.

9.2.2 Units of radiation

The unit of absorbed radiation dose is a Gray (Gy). A centigray (cGy) is a small fraction (1/100) of a Gy. Prior to the 1990's that unit of energy was referred to as a "rad".

9.3 Methods of delivery

9.3.1 External Beam/Teletherapy (*Tele* comes from the Greek for "far")

- Two-dimensional (2-D) external beam radiation is the most common form. Linear accelerators have mainly replaced cobalt-60 machines in most radiotherapy centers. Linear accelerators generate beams of photons and electrons and can emit megavoltage radiation. Cobalt-60 machines also deliver megavoltage radiation but the machines contain the radioactive material and require to be in thick concreted-walled rooms. Delivery of radiation is faster using a linear accelerator and therefore has obvious advantages in pediatrics.

- Three-dimensional (3-D) conformal and image modulated radiation therapy (IMRT), which allows visualization of radiation in three dimensions. Beams are focused from multiple areas to penetrate the tumor, making the actual radiation field smaller with less "scatter" and damage to normal tissues.
- Stereotactic radiosugery and stereotactic radiation: Stereotactic radiation can be performed as radiosurgery, where multiple beams converge at a point to deliver high dose of radiation to a small area of tumour. This is done as a one time treatment and produces a high degree of tumour necrosis. Tumours must be well circumscribed, < 4 cm in size, and not involve critical structures, such as the brain stem. This type may be carried out using either a linear accelerator or a system frequently referred to as a "Gamma knife" procedure (Swift 2002). For brain tumors, a fixed head frame is secured to the head to ensure precise delivery of the radiation beam. Stereotactic radiotherapy is similar to radiosurgery, but is carried out over multiple fractions and can treat larger tumor volumes. Again, a removable head frame is used to ensure precision of treatment.
- Intraoperative radiation is performed in a fashion similar to radiosurgery, except it is done when the tumour bed is exposed during surgery. It allows a precise treatment field, a higher dose, and potentially less side effects.

9.3.1.1 Fractionation

Fractionation is the process of radiotherapy delivery that divides the total dose into daily doses. The total dose determines the length of treatment. Treatment is normally given Monday to Friday. Fractionation provides better tumor control for a given level or normal tissue toxicity than a single large dose.

Fractionation spares normal tissues because of:

1. the repair of sublethal damage between fractions
2. cellular repopulation.

The normal 2 day rest each week provides time for normal cells to recover.

Tumour damage is increased because of:

1. reoxygenation
2. reassortment of cells within the cell cycle.

However, protracted courses of small doses of radiation may allow for malignant cell re-growth, as they have been given time to repair.

Hyperfractionation is further dividing the daily dose into 2 doses, usually with 6-8 hours between the 2 treatments. Theoretically higher doses may be given with less toxicity and greater tumor cell kill. This technique has been studied for several years and for some tumors, such as brain stem gliomas, no benefit has been found (Mandell et al 1999; Neider et al 1999). Research continues using this technique.

9.3.1.2 Total Body Irradiation (TBI)

The purpose of TBI is to cause bone marrow aplasia, that is to empty out the marrow cavity to allow for new stem cell growth. This is often the preparation for stem cell transplant. It is the aim that TBI will also eradicate malignant cells in sanctuary sites and/or minimal residual disease i.e. it has an antileukemic/antitumor effect.

After TBI, the patient would die of overwhelming infection if stem cells were not given. All organ systems at risk for side effects. TBI is usually given in fractionated doses twice a day for 4 to 5 days.

9.3.2 Interstitial implants/brachytherapy (Sealed source) (*brachy* comes from the Greek for "short distance")

Interstitial implants are isotopes provided as individually customised "seeds or pellets" that are inserted directly into a body cavity, either close or in contact with the target tissue. They provide a high dose of radiation to a very localised area, while having minimal damage to normal tissue. They may be placed for several days or left permanently in place. Most common uses are for gynecological cancers and supratentorial brain tumors in adults. In children, interstitial implants may be used in retinoblastoma lesions within the eye and removed 72 hours later. Also, in pelvic rhabdomyosarcomas, external beam radiation would have to travel through growing bones and intestines of the child. This could result in major growth retardation. Brachytherapy can minimize the dose delivered to surrounding normal tissue.

9.3.3 Unsealed source of radioisotope

A radioactive isotope is attached to a metabolite or an antigen-specific antibody, for example: iodine-131 – metaiodobenzylguanidine (^{131}I-MIBG). An MIBG scan, using a dye which is taken up by catechoanergic cells, is also useful for diagnostic purposes in children with neuroblastoma in identifying metastases, but this is not available at all centres. I-MIBG is a norepinephrine analog that concentrates in adrenergic tissue and therefore holds promise for cell-specific treatment of neuroblastoma. The MIBG can be labelled with radioactive isotopes of iodine, suitable either for diagnostic imaging or therapy. This is targeted radiotherapy.

9.3.4 Treatment planning

In the delivery of external beam radiotherapy there must be assured accuracy of:

- Dose
- Intensity
- Direction of beam
- Target area.

This will ensure that there is maximum damage to tumour cells with minimal damage to normal, surrounding tissue.

Treatment planning involves:

1. Accurate tumour imaging often using CT scans or MRIs. This outlines a treatment field so that measurements can be collated in order to ascertain the most appropriate form of radiotherapy and the shape and angle of the beams that would be necessary. Margins for treatment are identified that include the tumour and an area of surrounding healthy tissue; this accounts for microscopic tumour extension (Hopkins 1999). Consideration must be given to: limitations of imaging investigations, characteristics of the type of radiation used, and slight changes in body positioning.
2. Determining the dose of radiation energy. This is dependent on protocol, tumour histology and clinical assessment.
3. Identifying the type of radiotherapy. The depth of penetration of the radiation must be considered.

9.3.5 Simulation

Simulation is the process of developing a treatment plan. When planning the shape and angle of the beam it is vital that these factors are simulated with diagnostic radiographic imaging that uses a fluoroscopic unit (Hopkins 1999). This technique uses computer generated fields and simulates the specific number/angle of beams directed at the tumor. Physics calculations enable a computer to simulate the radiation beams that will be delivered.

9.3.6 Protection of health care professionals

Due to the risk of radiation damage to all cells, staff must be protected from any unnecessary exposure. Radiotherapy departments are legally obliged to appoint a radiation protection officer and follow stringent guidelines for radiation monitoring and protection (Byrne 2000). Radiography and radiotherapy staff, and staff caring for patients receiving brachytherapy or unsealed sources of radiation treatments, must wear badges that contain radiographic film that records the cumulative amount of radiation exposure per month.

9.4 Potential side effects

The side effects of radiation therapy are directly related to the amount of radiation received and the location of the field, age of child (younger children more vulnerable to side effects) and adjunctive chemotherapy.

Side effects can be:

- Acute: Acute side effects usually occur within the first few weeks of radiation therapy and are manifested in fast-growing cells located in the radiation field, such as the skin or oral mucosa.

- Delayed (sub)-acute: Delayed acute effects can occur weeks to months after completion of treatment. These are both self-limiting and resolve with time.
- Late: Late effects are the result of irreversible damage. The risk of secondary tumors in the radiation field is also a significant late effect of radiotherapy.

Part 4 of the book will detail the side effects of treatment.

9.5 Special considerations

9.5.1 Ensuring accuracy of treatment: Patient issues

Following planning, the delivery of the angles of the beams must be maintained throughout every treatment. Radiation energy decreases over distance and the energy decreases uniformly along the path. It is therefore possible to calculate the distance the child must be from the radiation source in order that the correct dose is received. Identical body positioning is essential.

9.5.1.1 Marking

External markings using ink or tattoo are applied to the patient's skin to mark the positioning field. These are not easily removed. DO NOT REMOVE markings! If the markings fade the radiographers may need to re-draw the lines. *If the marks fade, while on weekend leave, the family should be asked to redraw over the marks using a different colour of felt tip pen. This will enable the radiographers to distinguish between the two (Hopkins 1999).*

9.5.1.2 Patient immobilisation

Various methods of immobilisation are applied often dependent on the area of the body to be treated. When treating brain tumours or head and neck tumours, a shell is made for individual use to ensure that the head is immobilised. The shell is an exact fit and even small movements will be restricted. These immobilization shells/moulds are also used to reproduce positioning of the child over consecutive treatments. These moulds may sometimes be frightening to the child, depending on his or her developmental level. Developmentally appropriate explanations should be given to the child during radiation planning (McGuire Cullen et al., 2002). To ensure the accuracy and safety of the delivery of radiation treatment, it is also essential during the planning stages to assess the child's ability to cooperate.

Other immobilisation techniques include:

- Head rests, knee rolls
- Vacuum bean bags filled with Styrofoam beads
- Development of immobilizers/blocks
- Plaster of Paris casts.

9.5.1.3 Sedation and general anaesthesia

Because of consecutive days of being unable to eat prior to radiation, the nutritional status of children receiving sedation for radiation should be monitored closely. When possible, it is often best to treat sedation cases early in the morning.

Children may require sedation due to young age, developmental immaturity or extreme distress. Sedation methods range from a mild antianxiolytic to conscious sedation or a short-acting general anesthetic. Short acting drugs such as ketamine may be used. These children will require to be treated early in the day to avoid repeated extended periods of fasting. Hydration and nutrition will need particular attention.

If the child is anaesthetised, an anaesthetist must be present to monitor the child. This will be with the aid of audiovisual monitoring and the electrocardiographic and respiratory monitors for the short period that the child requires to be alone when the radiation treatment is being delivered. Another point to consider is that radiotherapy is usually delivered to children in an adult centre. Adequate, safe recovery must be assured.

If the child requires another procedure such as lumbar puncture, the team will often organise to have these procedures carried out with the same anaesthetic.

9.5.1.4 Preparation of children and young people

Receiving radiation therapy can be a very frightening ordeal. Good preparation will help elicit children's cooperation. Young people may also not be willing to cooperative if they are not adequately informed and prepared for the process involved. Parent's anxiety can also impact the child's anxiety. It may be stressful for everyone that the child is left in the room alone.

9.5.2 Brachytherapy

Although rarely used it may have significant advantages in children and young people due to significant local control and fewer late effects. Initially the mould may need to be inserted or stitched in place using a general anaesthetic.

9.5.3 Unsealed sources of radiation treatment

^{131}I-MIBG is given intravenously under extremely protected conditions. Patent venous access is imperative. The ^{131}I-MIBG contains a specific radioactive isotope of iodine.

Protection of the thyroid gland is imperative. Oral iodine is administered before, during and after the radioactive material is given. This ensures saturation of the thyroid gland with non-radioactive iodine.

All body tissues become radioactive. Therefore all bodily fluids must be handled as radioactive waste (Hopkins 1999). This leads to the need for extreme caution in the care of a child. Unfortunately, the child's contact with family must be kept to a minimum.

9.6 Future Perspectives

There have been several recent advances in the field of radiation oncology. The goal of the research is to deliver the highest tolerated amount of radiation while decreasing exposure to surrounding normal tissue. Several techniques have been developed to reach this goal. Proton radiation therapy is the newest technique that delivers a large dose to the tumor and a smaller dose to normal tissue (Tarbell and Kooy, 2002). The advances in radiation therapy are decreasing side effects, but the cost to update and create new equipment limits the availability of new radiation treatments.

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