Radiation Therapy

Introduction

- X-rays were discovered by Roentgen in 1895
- Called “x-rays” because their etiology was unknown at the time
- Roentgen’s apparatus was simple: vacuum tube and electric current

Introduction

- In 1896, a physicist named Becquerel discovered that certain substances could emit x-rays (i.e. uranium)
- Marie Curie became interested in Becquerel’s work and discovered radium

Introduction

- Biologic effects of radioactive materials soon became evident
- Lab workers developed erythema of the hands following work with x-ray tubes
- Eventually, carcinomas developed on the fingers, hands, and arms of these workers

Introduction

- Use of x-rays expanded to many fields of medicine
- X-rays were used help identify the location of foreign objects in the body prior to surgery
- In one experiment, a 45 minute exposure to the skull was used, resulting in dramatic alopecia

Introduction

- Becquerel carried a tube of radium given to him by Marie Curie in his vest pocket
- 2 weeks later, he developed an intense inflammatory response where the radium had been
- This led to the first radiation treatments to the skin by direct application of radium

Introduction

- The first use of radiation to treat a skin disorder was in 1900 (squamous cell carcinoma on the nose)

Introduction

- Alexander Graham Bell is credited with the idea of "implanted" radiation therapy
- First used for cervical cancer in the 1903/1904 with very good results, and similar techniques are still used today
- Use limited by availability and cost of radium (1 g cost over $100,000 in early 1900s)

Introduction

- The development of radiation therapy by external beams was much slower
- Early treatments resulted in significant necrosis of treated tissues
- Biologic experiments showed that the dosage could be divided into many smaller treatments with fewer side effects (this is the concept of **fractionation**)

Introduction

- Safety was not a great concern in the early days (family, friends, and physicians were in the room during treatment!)
- Eventually, adverse effects were noted, and shielding of the patient and medical personnel began

Introduction

- At first, dose monitoring was inexact and was measured by skin erythema
- In 1928, the roentgen, a unit of radiation exposure, was defined and put into use
- In the 1950s, cobalt machines were developed, and radiation therapy entered the modern era
- Developments are still occurring!

Introduction

- At one point, dermatologists were trained in how to administer radiation therapy, and many had devices in their office for this purpose
- As more and more dermatologic therapies have become available, and as the effects of chronic radiation have been studied, radiation therapy has been used less frequently

Introduction

- Although dermatologists no longer administer radiation therapy, we are involved in the diagnosis of skin disorders and in determining the best treatments for our patients, and therefore a knowledge of radiation therapy is essential

Radiation Physics

- What is an x-ray?
  - Part of the electromagnetic spectrum
  - Very short wavelength
  - X-rays behave like continuous waves, but also like discontinuous particles (photons)

Radiation Physics

- When an x-ray hits an atom, the photon bumps into an electron and knocks it from its orbit around the nucleus
- The atom is now an ion (charged particle); hence x-rays are called “ionizing radiation”

Radiation Physics

- Not all components of the electromagnetic spectrum can ionize an atom, just those with high enough energy (short wavelengths)
- For example, UV light can damage DNA structure, but does not have enough energy to dislodge electrons

Radiation Physics

- Radiation therapy uses the ionizing ability of x-rays to induce a biologic effect
- It is the effect on DNA that is responsible for the cancer-fighting effects of x-rays

Radiation Physics

- The energy of an x-ray is measured in units called electron volts (eV)
  - Radiation therapy uses high numbers of electron volts, and the terms keV (thousands of eV) and MeV (millions of eV) are often encountered
- Low energy x-rays are used routinely in radiology

Radiation Physics

- In the early days of radiation therapy, only low energy x-rays were available, and these are preferentially absorbed by bone
- Modern high energy machines avoid this problem of bone absorption

Radiation Physics

- How are x-rays generated?
  - From naturally occurring or man-made radioactive substances (radionuclides)
    - Radium
    - Cesium
    - Cobalt
    - Iridium
    - Iodine
    - Palladium

Radiation Physics

- Radium was used frequently in the past, but it has a half life of 1600 years and decays to radon gas and lead, and now much safer compounds are used

Radiation Physics

- Cesium is used for treatment of gynecologic cancers
- Iridium and iodine are the most frequently used radionuclides for brachytherapy (implantation)
- Iodine is used for permanent implantation in the prostate gland and in the choroid of the eye (ocular melanoma)

Radiation Physics

- Palladium is used like iodine for ocular implantation
- Cobalt is a source of high energy gamma rays for use in external beam treatment machines

Radiation Physics

- In addition to x-ray formation by certain substances, machines have been created that generate x-rays

Radiation Physics

- Roentgen: his machine created x-rays by heating a charged filament (cathode) and releasing the electrons that formed towards a positively-charged anode
- The electrons strike a metal plate at the anode, and their kinetic energy is emitted as x-rays
- Lead casing directs the x-rays in the desired direction

Radiation Physics

- Tubes that produce x-rays with energies of 40-120 keV are used for diagnostic radiographs
- Tubes that produce 120 to 300 keV are used for radiation therapy (this is relatively low energy with most energy absorbed by the skin, hence the use in treating skin cancers)

Radiation Physics

- Early x-ray machines produced x-rays of 100,000 eV (100 keV, which is relatively low energy)
- These low energy rays are absorbed mainly by the skin, resulting in treatment-limiting skin reactions

Radiation Physics

- The advent of the cobalt (high energy > 1 MeV) machine in the 1950s was an important advance in radiation therapy, allowing relative sparing of the skin during treatment for deeper cancers

Radiation Physics

- Modern high energy machines can produce 1,000,000 eV (1 MeV), which results in maximum energy levels <u>below</u> the surface of the skin (about 0.5 to 3.0 cm, depending on the energy of the beam)
- Complicated physics explanation for this, and just understand that higher energy waves penetrate deeper

Radiation Physics

- Linear accelerator:
  - In essence, electrons are rapidly accelerated to near the speed of light
  - The acceleration follows a linear path, hence the term “linear accelerator”
  - The electrons strike a target, and high energy x-rays are emitted

Radiation Physics

- Linear accelerator
  - Creates a high energy beam
  - Edges of beam are sharply defined (precise)
  - An electron beam can be generated for superficial skin treatments
  - Dose of radiation and field size can be regulated, allowing large fields for total skin/total body treatments

Radiation Physics

- How is radiation measured?
  - Early on, skin erythema was observed and thought to correlate to radiation dose
  - But, individual responses vary, and this method is imprecise

Radiation Physics

- How do we measure radiation?
  - Roentgen (R): a unit of radiation exposure defined in 1928
  - Measures the ability of a beam of radiation to ionize air
  - A more uniform and reproducible unit than skin erythema

Radiation Physics

- How do we measure radiation?
  - Rad: unit of *r*adiation *a*bsorbed *d*ose (biologically relevant)
  - 1 rad = 100 ergs of energy absorbed per g of tissue
  - Gray (Gy): 100 rads
  - Centigray (cGy): 1 cGy = 1 rad (older term)

Biologic Properties of Radiation

- Very complex subject, much of which remains undiscovered
- For our purposes, we can review the effects of radiation on normal tissues and on tumors

Biologic Properties of Radiation

- Radiation causes ionization in biologic materials, and DNA is the most important target and is the key to the biologic effects of radiation
- Other targets exist, of course, and the effect of radiation on these targets contributes to the biologic changes that are seen

Biologic Properties of Radiation

- X-ray photons can directly damage DNA, often with a lethal result for the cell
- Indirect effects of radiation are much more common:
  - Water is readily ionized, creating reactive hydroxyl radicals, peroxides, and oxygen radicals
  - These species then interact with and damage DNA

Biologic Properties of Radiation

- Not all DNA damage is lethal to a cell, for many repair mechanisms exist
- Double strand DNA breaks appear to be the most damaging
  - Unrepairable → cell death
  - Repaired with errors → cell death or mutation or no effect
- Uncoiled DNA is much more susceptible to damage (seen in early S phase of cell cycle)

Biologic Properties of Radiation

- It may take several cycles for the cell to die; hence, rapidly dividing cells will show radiation damage sooner than slowly dividing cells
- Consider the effects of radiation on mucosal (rapidly-dividing) cells vs. brain (very slowly-dividing) cells

Biologic Properties of Radiation

- Some cell types (lymphocytes and germ cells, some mucosal and parotid gland cells) die almost immediately after radiation exposure
- This is likely due to apoptosis (programmed cell death via p53 and p21)

Biologic Properties of Radiation

- Sensitivity of malignant tumors to radiation varies based on cell type
- Highly responsive tumors include:
  - Hodgkin's and non-Hodgkin's lymphomas
  - Seminoma and germinoma
  - Neuroblastoma
  - Retinoblastoma
  - Small cell cancers

Biologic Properties of Radiation

- Moderately responsive tumors include:
  - Head and neck cancer
  - Breast cancer
  - Prostate cancer
  - Cervical cancer
  - Lung cancer
  - Rectal cancer
  - Esophageal cancer

Biologic Properties of Radiation

- Poorly responsive cancers include:
  - Melanoma
  - Glioblastoma
  - Renal cell carcinoma
  - Pancreatic carcinoma
  - Sarcomas

Biologic Properties of Radiation

- The effects of radiation on normal tissues are often the limiting factor in treatment
- For example, radiation-responsive tumors (i.e. lymphoma) can be controlled or cured with minimal damage to adjacent normal tissues
- Poorly responsive tumors may require high doses of radiation, hence with more side effects to the surrounding tissues

Biologic Properties of Radiation

- The balance between control/cure and side effects must be weighed in any medical or surgical treatment
- Even appropriately designed treatments can result in undesirable side effects

Biologic Properties of Radiation

- Acute radiation effects:
  - Lethargy and fatigue
  - Mucositis
  - Esophagitis
  - Pneumonitis
  - Hepatitis
  - Nausea, vomiting, diarrhea
  - Dysuria
  - cytopenias

Biologic Properties of Radiation

- Acute cutaneous effects include:
  - Erythema
  - Pruritus
  - Dry and moist desquamation

Biologic Properties of Radiation

- Treatments include:
  - Observation
  - Topical steroids for pruritus
  - Drying agents for moist desquamation
  - Silvadine cream

Biologic Properties of Radiation

- Late effects of radiation may be due to loss of small vessels with resultant fibrosis and subsequent organ dysfunction

Biologic Properties of Radiation

- Carcinogenesis is an established risk, related to DNA damage and misrepair
- Occurs 5-10 years after treatment
- Leukemias, breast, and thyroid cancers are the most commonly induced malignancies
- Age at the time of radiation is a factor

Clinical Applications

- Fractionation of treatment:
  - Early treatments were given in a few large doses, resulting in tumor eradication but significant tissue necrosis
  - Dividing the treatments results in tumor control with much less damage to normal tissues
  - This is the reason why many treatments are divided into 25 to 35 sessions over 5 to 7 weeks

Clinical Applications

- Total radiation dose:
  - Dose-response data has been gathered mainly from retrospective studies
  - Basically, increasing the total dose delivered results in higher rates of local control and cure
  - Typically, as high a dose as can be tolerated is delivered

Clinical Applications

- Total radiation dose:
  - Assuming that a larger tumor (more cells) requires a higher dose of radiation to achieve control, smaller tumors (fewer cells) should in theory require smaller doses
  - "shrinking field technique": radiation field size is reduced as the tumor shrinks, thus minimizing adverse effects in surrounding tissues

Clinical Applications

- Treatment time and fraction size:
  - For a given total radiation dose, a shorter treatment time (i.e. 4 weeks vs. 5 weeks) results in more acute toxicity
  - Longer treatment times mean less dose per treatment, limiting the late effects of radiation
  - Treatments delivered too slowly may result in *accelerated* tumor growth

Clinical Applications

- In summary:
  - Radiation oncologists design treatments to give the maximum tolerated dose over a period of time that allows minimizing acute and late effects on normal tissues while allowing for adequate tumor control/cure

Treatment Process

- The first step is treatment planning, often with a multidisciplinary approach
- “target volume” must be determined
  - Tumor itself
  - Adequate margin
  - Consideration of areas at risk for local spread
  - Patient variables (positioning, movement with breathing)

Treatment Process

- 3 dimensional imaging is key, and this can be performed initially with a machine called a simulator
- The simulator resembles a linear accelerator, but uses much lower energy to produce a diagnostic image
- CT scanning is used in conjunction with the simulator

Treatment Process

- The CT images are used in a planning computer, and the tumor volume and adjacent normal tissues are outlined
- The treatment plan is then prepared, including the size and shape of the field, the angle of radiation delivery, dose and fractionation
- On average, this can take 4 to 30 hours!

Treatment Process

- The average daily treatment session lasts 10-20 minutes
- Much of that time is spent in preparation and positioning
- Custom-made body casts or masks can help exactly duplicate the patient’s position from day to day
- Total radiation exposure time is 1-2 minutes

Treatment Process

- Skin cancer treatment:
  - Bolus: tissue equivalent material placed on the surface of the skin overlying the treatment area so that the maximum radiation dose is delivered at the skin surface

Goals of Therapy

- Definitive tumor treatment (cure)
- Organ preservation in lieu of radical surgery
- Increase local/regional control following excision of primary tumor
- Palliation of symptoms from primary or metastatic disease

Radiation Therapy for Dermatologic Conditions

- Radiation therapy is no longer routinely used for the treatment of benign skin disorders, but its use may be considered in disorders not responsive to other therapies (often only after the failure of all other therapies)

Radiation Therapy for Dermatologic Conditions

- Radiation therapy is no longer used for tinea capitis, warts, acne, or hemangiomas, having been replaced with far more effective and safer treatments

Radiation Therapy for Dermatologic Conditions

- Actinic Keratoses
  - In some cases, Grenz rays may be used for the treatment of AKs
  - Many other safer and better techniques exist!

Radiation Therapy for Dermatologic Conditions

- Bowen's disease and erythroplasia of Queyrat
  - Can be treated with Grenz rays, using a higher dose than for AKs
  - Inflammatory reactions in the genital are expected

Radiation Therapy for Dermatologic Conditions

- Lentigo maligna
  - Radiation therapy is very good method for treating lentigo maligna on the face of an elderly patient
  - Some reports suggest cure rates similar to surgical excision
  - An adequate margin and sufficient depth (to include hair follicles) should be included

Radiation Therapy for Dermatologic Conditions

- Basal and squamous cell carcinomas
  - Radiation therapy is an accepted treatment for these lesions
  - Individual treatment plans can be designed based on the size, site, depth, and histology of the tumor
  - Condensed courses (i.e. 2-3 sessions per week with higher dose per session) can be designed for frail patients

Radiation Therapy for Dermatologic Conditions

- Basal and squamous cell carcinomas
  - Dispersed pattern and poorly differentiated tumors have higher recurrence rates
  - Recurrent or incompletely excised tumors can be treated with radiation
  - Cure rates up to 95% have been reported
  - Cosmetic results (short term) are good

Radiation Therapy for Dermatologic Conditions

- Paget’s disease
  - Intraepidermal neoplasm may be treated with radiation

Radiation Therapy for Dermatologic Conditions

- Merkel cell carcinoma
  - High rates of local recurrence and lymph node and distant metastases
  - Radiation therapy is often added to surgical excision to increase local control and reduce the risk of metastatic disease

Radiation Therapy for Dermatologic Conditions

- Cutaneous lymphomas
  - Lymphomas are highly sensitive to radiation
  - Therapy is often curative for B cell and CD30+ lymphomas
  - Extent of skin involvement and depth of the tumor determine which treatment is given

Radiation Therapy for Dermatologic Conditions

- Kaposi’s sarcoma
  - Classis KS can be treated with electron beam or superficial radiation
  - AIDS-associated KS can also be treated, but lesions may take longer to resolve, and local edema is more common

Radiation Therapy for Dermatologic Conditions

- Angiosarcoma, metastatic disease to the skin, and leukemic infiltrates of the skin may also be treated with radiation

Radiation Therapy for Dermatologic Conditions

- Electron beam therapy
  - Electrons lose energy rapidly upon penetrating the skin (energy decreases in a linear fashion relative to depth)
  - Superficial penetration of electrons allows skin-directed therapy
  - Energy of the electron beam can be altered to vary depth of penetration

Radiation Therapy for Dermatologic Conditions

- Electron beam therapy
  - A bolus can be used to focus the beam's energy on the skin surface
  - X-rays often contaminate the electron beam, with higher amounts at higher energy, and total x-ray radiation dose must be calculated
  - This is of importance with "total skin electron beam therapy (TSEB)" for CTCL

Radiation Therapy for Dermatologic Conditions

- Electron beam therapy
  - Used in the treatment of CTCL (mycosis fungoides)
  - Any stage may be treated, but most commonly used for patch/plaque lesions or for erythrodermic patients
  - Tumors may be treated with supplemental doses
  - 4-6 MeV beam
  - Treatments 4 days per week for 9 weeks

Radiation Therapy for Dermatologic Conditions

- Electron beam therapy
  - Typically no systemic side effects, since the radiation dose is limited almost entirely to the skin
  - Acute cutaneous side effects include erythema, pruritus, edema, onycholysis, and xerosis
  - Chronic effects include pigment change, telangiectasias, atrophy, alopecia, and hypohidrosis

Basic Terminology

- Radiation:
  - Emission of energy
  - This energy can be used to induce a biologic effect, hence the use of radiation therapy for the treatment of skin conditions
- Curie (Ci) and Becquerel (Bq):
  - Units of radioactivity

Basic Terminology

- Rad:
  - Unit of measurement for the dose given to the patient
  - The tern “Gray” is more commonly used
- Gray (Gy)
  - Unit of radiation dose
  - 1 Gy = 1 J/kg = 100 rads

Basic Terminology

- Photon:
  - Quantum of electromagnetic energy
- X-ray:
  - High energy photon
- Grenz ray:
  - Low energy X-ray
- Gamma ray:
  - Consists of high energy photons created by a nucleus (as opposed to a machine)

Basic Terminology

- Electron:
  - Small, negatively charged particle
- Alpha particle:
  - Helium nucleus (2 protons and 2 neutrons)
- Beta particle:
  - Electrons emitted by a nucleus as a byproduct of nuclear decay

Basic Terminology

- Linear accelerator:
    - Device that accelerates charged particles (typically electrons), creating photons when the charged particles strike a target within the machine
- Half life:
    - Time needed for a radioactive material to decay to ½ of its original activity