Disclosures

• Disclosures: None
Outline

• Goals of cancer therapy
• Goals of radiation therapy
• Basics of radiation oncology
  – Radiation Physics
  – Radiation Biology
  – Radiation Therapy
  – Patient presentations
• The future of radiation oncology
Principles of cancer therapy

• Minimize therapy
  • Toxicity, time, cost

• Minimize negative impact on quality of life
  • Toxicity, function, cosmesis

• Improve quality of life
  • Palliation, organ preservation

• Maximize impact on quantity of life
  • Cure and remission

• Improve outcomes
  • Research
Radiation Oncology

The discipline of radiation oncology

Radiation Biology

Physics

E=mc²

Radiation Therapy
The Physics of Radiation Oncology

Just the basics
What is radiation?

- “the complete process by which energy is emitted by one body, transmitted through an intervening medium or space, and absorbed by another body.”
Types of Radiation
The Electromagnetic Spectrum

The electromagnetic spectrum

- Energy (kcal/mol)
  - Nuclear excitation
  - Core electron excitation
  - Electronic excitation
  - Molecular vibration
  - Molecular rotation

- Frequency (ν) in Hz
  - 10^19
  - 10^17
  - 10^15
  - 10^13
  - 10^10
  - 10^5

- Wavelength (λ) in µm
  - 10^-6
  - 10^-4
  - 10^-1
  - 0.4
  - 0.8
  - 2
  - 10^2
  - 10^6
  - 10^10

- Cosmic rays
- γ-rays
- X-rays
- Ultraviolet light
- Visible light
- Infrared radiation
- Microwaves
- Radio waves
  - NMR
X Rays

How are x rays generated?
The Linear Accelerator

The linear accelerator

- High energy photons and electrons
- Uniform beam characteristics
- Precise field shaping
- Precise delivery
  - The gantry rotates
  - The couch rotates
  - The patient is immobilized
Radiation Therapy Basics

- GTV = Gross tumor volume
- CTV = Clinical target volume; typically margin added for microscopic extension; may be limited at anatomic boundaries
- PTV = planning target volume; isotropic margin to account for ‘set up uncertainty’
- ITV = internal target/tumor volume; volume drawn accounting for organ or tumor motion
Radiation Planning Techniques

- **3D CRT**
  - Use CT to plan from anatomy, allows freedom of multiple angles
  - “Virtual patient”

- **IMRT**
  - Dose cloud, complex
  - Inverse planning
Intensity Modulated Radiation Therapy

- Modulation of the intensity across each beam
- Allows customization based on a specific planning objective
  - Treat tumor to 50Gy, keep bladder dose below 20 Gy.
Intensity Modulated Radiation Therapy

Intensity modulated radiation therapy

Enables use of higher and more sculpted tumor dose
Volumetric modulated arc therapy

Volumetric Modulated Arc Therapy (VMAT)

- Linac moves and can deliver dose in 360 arc around patient
- Quicker treatment delivery
- More conformal for moderate dose of prescription
- Improved dose homogeniety
- More low dose to surrounding tissues
Brachytherapy

• Placing a radiation source inside or adjacent to the tumor

• Rapid dose fall-off allows maximal sparing of normal tissues (no “going trough” normal tissue to get to the tumor)

• Used commonly for tumors
  – in body cavities (cervix, endometrium, vagina, nasopharynx)
  – close to the surface (prostate, sarcoma, tongue, lip, breast)
Plaque Simulator Isodose Plot
High Dose Rate Branchy

High dose rate brachy (HDR) Example – Ring and Tandem

Used to treat cervical and endometrical cancer
Stereotactic Radiosurgery

- Historically used to treat brain tumors (Gamma Knife)
- Technology has developed where we can now treat tumors in other body sites (Stereotactic Body Radiation Therapy)
  - Lung
  - Liver
  - Bone
- Cyber knife is a brand of machine that delivers stereotactic radiosurgery
Radiation Biology
Radiation Survival Curve

Radiation survival curve
Fractionation

Rationale: take advantage of the slightly improved survival of normal tissue to smaller doses, amplified over many treatments.
The 4 “R”s of fractionated radiation

• Repair
  – Healthy cells repair DNA damage (so do tumor cells unfortunately)

• Reassortment (redistribution)
  – Radiation causes cells to accumulate in certain phases of the cell cycle

• Reoxygenation
  – Tumors reoxygenate after radiation

• Repopulation
  – Tumor and normal cells repopulate between doses of radiation
Repair

DNA is the primary target of radiation
- Indirect
- Direct
- SSB are repaired
- DSB are key!

Particles
Photons

Cells that correct DNA dsb go on to divide another day.....REPAIR.
Redistribution

Ionizing Radiation

<table>
<thead>
<tr>
<th>G1 Arrest</th>
<th>Cdk4/6</th>
<th>Phosphorylation of Serine-16</th>
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<td>p53</td>
<td>Apoptosis</td>
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<tr>
<td>Cell Cycle Arrest</td>
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<td>Accumulation in G1</td>
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<tr>
<td>Accumulation in G2</td>
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</tbody>
</table>

Radiation induces cell cycle arrest to repair DNA damage.....REDISTRIBUTION
Cell Cycle and Radiation Sensitivity

Cell cycle and radiation sensitivity

M > G2 > ES > LS  Redistribution into a sensitive phase can matter!
Reoxygenation

Following radiation, tumors reoxygenate rapidly........REOXYGENATION
Radiation Modifiers

- Dose (Gy)
- Tumor Control (%)
- Normal Tissue

60 Gy
- 65% Local Control
- 15% Normal tissue damage

60 Gy
- 75% Local Control
- 15% Normal tissue damage

Radiosensitization

DEF = 1.4
Radiation Modifiers

![Graph showing radiation modifiers with tumor and normal tissue dose response curves.](image)

- **Tumor Control (%)**
  - **Dose (Gy)**
  - **Tumor**
  - **Normal Tissue**

- **60Gy**
  - 65% Local Control
  - 15% Normal tissue damage

- **60Gy**
  - 75% Local Control
  - 15% Normal tissue damage

- **DEF=1.4**

Radiosensitization
Radiation Targets

- **Single Target Agents**
  - Growth factor receptors (EGFR, VEGFR)
  - DNA repair proteins (DNA-PK, Rad51)
  - Transcription factors (NFkB, p53)
  - Signal transduction proteins (Ras, PI3K, c-Abl)

- **Multi-target Inhibition**
  - Chaperone proteins (HSP90 inhibition)
  - Microenvironment (angiogenesis, vasculature)
  - Epigenetic modification

- **Radiation Inducible Targets**
  - Antigens or receptors (Fas, CEA)
Radiation targets
Issues for Target/Agent Development

• Mechanism
  – Cell type or condition specific

• Method of Targeting
  – Antibodies (EGFR, VEGFR)
  – Small molecules (Gleevec, Flavopiridol)
  – Gene therapy (TNFerade)

• Therapeutic ratio
  – Tumor > normal cells (Rad51)
Immunomodulatory agents

Immunomodulatory Agents

• Can be combined well with RT
  – Abscopal effect

• Types of agents
  – PD1
  – PDL1
  – Others
Abscopal Effect

Figure 1. Results of Diagnostic and Radiotherapy Simulation Imaging throughout the Disease Course.

Axial CT images are shown, corresponding to the timeline showing therapy and disease status. White arrows indicate the paraspinal mass, red circles indicate the right hilar lymphadenopathy and spleen, and black arrows indicate an incidental hepatic hemangioma. Panel A (top) represents the status before treatment with ipilimumab. Panel B shows enlargement of the paraspinal mass (top), stable right hilar lymphadenopathy (middle), and new splenic lesions (bottom). Panel C shows images 1 month after radiotherapy, when the response to radiotherapy had not yet occurred, with apparent continued worsening disease at all three sites. Several months after radiotherapy, the targeted paraspinal mass showed a response (Panel D, top). Furthermore, disease response outside of the radiation field was seen with decreased right hilar lymphadenopathy (middle) and resolution of splenic lesions (bottom). The response was durable, as shown in Panel E. Panel F shows the CT simulation image for radiotherapy planning, with the target volume (indicated in purple) encompassing the right paraspinal metastatic mass.
Radiation Therapy

Clinical practice
Goals of radiation therapy

• Cure
  – Cancer localized to one organ or region

• Palliation
  – Cancer disseminated to multiple organs that are causing bothersome symptoms
Indications for radiation therapy

- Cure
  - Prostate cancer
  - Other urologic cancers
  - Breast cancer
  - Lung cancer
  - Head and Neck Cancer
  - Gynecologic Cancers
  - Pediatric Cancers
  - CNS tumors
  - Skin cancers

- Palliation
  - Bone pain
  - Shortness of breath
  - Neurologic symptoms
  - Pain from a space occupying lesion
The Oncology Team

The oncology team

- Radiation Oncology
- Medical Oncology
- Primary Care
- Surgery
- Social work and Support services
- Radiology
- Other specialties
Develop a multimodality plan

• Surgery
• Radiation
• Systemic therapy
  – Chemotherapy
  – Targeted agents
• Other localized therapies
  – Focal ablation techniques
  – Focal drug delivery
The radiation therapy treatment process

- Following consultation visit
- CT simulation (planning session)
- Transfer of images to treatment planning system
- Fusion of outside images
The radiation therapy treatment process

- Contouring (normal structures, target structures)
- Creation of plan (dosimetry)
- Evaluation of plan (by MD)
- Evaluation of plan (by physics)
- Transfer of plan to treatment machine
- Treatment delivery
Patient Presentations
The treatment process – Patient A

- Develop a treatment plan (multimodality)
- Determine the appropriate RT modality
- Identify a target
- Identify surrounding normal tissue at risk
- Create a treatment plan (radiation)
- Deliver the treatment
- Follow the patient
Patient A

- 55 yo F with new lump in her left breast
- Suspicious abnormality on mammogram
- Biopsy consistent with infiltrating ductal carcinoma
- No family history of breast cancer
Develop a treatment plan

- Treatment options
  - Mastectomy
  - Breast Conserving Therapy (lumpectomy + RT)
Patient A

• Selects breast conservation
• Lumpectomy and sentinel lymph node biopsy
• Pathology reveals a 3 cm tumor and 4 axillary lymph nodes
• The patient receives chemotherapy
• Returns to radiation oncology
Determine the RT Modality

- External beam radiation
  - Protons
  - Photons
  - Electrons

- Brachytherapy
  - Sealed sources
  - Unsealed sources
Identify the target and normal tissue - Simulation
Create A Plan

Create a plan
Deliver The Treatment

Deliver the treatment
Patient B

- 54 yo M with an elevated PSA on routine exam
- No prior medical problems
- Biopsy consistent with adenocarcinoma of the prostate, Gleason score of 6
Develop a treatment plan

- Surgery
- Surgery and radiation (based on surgical findings)
- Radiation
  - Brachytherapy
  - External beam RT
  - Combination
- Radiation and hormonal therapy
Create A Plan

Create a plan
Image Guided Radiation Therapy

Image guided radiation therapy

- Calypso
- Gold fiducial markers
Image
Deliver the Treatment

Deliver the treatment
Is it all just that easy?

- Normal tissue toxicity
  - Acute effects
  - Late effects

- Stem cell depletion, chronic oxidative damage, vascular destruction, fibrosis, and more

- Radiation is dosed to normal tissue, NOT tumor!
Lung - Fibrosis
Lymphedema
Mucositis

Mucositis – stem cell depletion
Where do we go from here?
The future of radiation

• Biology
  – Use radiation to induce targets for other agents
  – Better radiation sensitizers and protectors
  – Combining radiation and targeted drugs

• Physics
  – Improved targeting (imaging)
  – Improved delivery methods (equipment)

• Clinical
  – Translate exciting laboratory findings into the clinic
  – Continue to develop clinician-scientists
Why Protons Can be Superior to Photons

- **Protons**
- **X-rays do not stop**
- Excess radiation to healthy tissue results in potentially costly side effects and secondary tumors.
Proton Therapy

Proton Therapy Delivers Less Heart & Lung Dose

- X-Rays Deliver Excess Radiation
- Resulting in
  - Coronary Artery Stenosis
  - Secondary Cancer
  - Lung Fibrosis
Maryland Proton Treatment Center

Maryland Proton Treatment Center (MPTC) – A Regional Resource to Mid-Atlantic Healthcare Providers

- $200 million, 110,000 square feet, 5 treatment rooms, with unique patient throughput process enhancing patient volume capacity allowing treatment of up to ~1900 patients/year (150-190 patients/day)

VISION

To become a Proton Center of Excellence across all academic missions, accessible to and in PARTNERSHIP with major regional Health system/Oncology providers
Take home messages

• Radiation is a tool used in cancer therapy
• Radiation causes DNA damage, which can lead to cell death
• The effects of radiation can be altered by modifying physical factors, physiologic factors, fractionation, drugs, and other variables
• Radiation can cause complications
• Radiation is INTERESTING!