Proton therapy for Gastrointestinal tumors

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Disclosures

• Ed Kim has no financial relationships, arrangements, or affiliations with commercial entities.

Radiation Therapy

- Use of radiation to cause DNA damage inside tumor cells → cell death
- Relies on oxygen
- Generation of free radicals
- Normal cells are able to repair this damage

Therapeutic Ratio

"Rules" in Radiotherapy

- Radiation damage is non-specific
- Cure and complication probabilities are dose- and volume-related
- Hit the tumor: as hard as possible, as much as possible
- Avoid surrounding normal tissues
  - “Side effects (from radiation) do not occur on non-irradiated tissues” - Herman Suit
- Radiation enters the body, depositing majority of dose near surface
- Radiation exits the body

Radiation oncology is a technology based specialty

- Radiation treatment capabilities change constantly.
- Radiation planning and delivery is technology driven.
  - As computer technology changes, so do radiation planning and delivery capabilities.
The Evolution of Radiation Therapy

1960's: The First Clinac
- Standard Collimator
- The Clinac reduced complications compared to Co60

1970's: Cardiod Blocking
- Electron Blocking
- Blocks were used to reduce the dose to normal tissues

1980's: Multileaf Collimator
- Dynamic MLC and IMRT
- MLC leads to 3D conformal therapy which allows the first dose escalation trials.

1990's: High resolution IMRT
- IMRT Evolution evolves to smaller subfields and high resolution IMRT along with the introduction of new imaging technologies

2000's: Functional Imaging
- IMRT evolution to smaller and smaller subfields and high resolution IMRT

Classic 2D planning
- Required large treatment fields because of limited accuracy.
- Larger fields → higher dose to normal tissue → more side effects
- Used plain films to localize target volume
- Couldn’t account for volume changes or inhomogeneities

2D planning
- Standard Collimator
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3D planning
- CT based planning
- Uses conformal fields with greater accuracy
- Smaller fields allow higher doses to target with lower doses to normal structures
- Intensity Modulated Radiation Therapy (IMRT)
- Allows sculpting of dose around normal structures

3D treatment planning

3D-CRT
Intensity Modulated Radiation

- More complex planning, allows better sculpting of dose around sensitive tissues

Linear accelerator (LINAC)

- These advances are built upon the limitations and physical properties of photons / x rays.

What about protons?

- Charged particles
- Used medically since 1950s
- Over 90,000 pts treated with protons worldwide
- Unique physical properties of protons allow sparing of normal tissue
What is proton therapy?

“Radiation therapy with brakes”

Normal Tissue

Proton Radiation

- Heavy charged (positive) particle
- Direct DNA damage
- Biologically as effective as photons
- But... they know when to stop

Why protons are different than x-rays

In order to deliver the same dose to the tumor, x-rays (photons) must deposit a greater dose of radiation to healthy tissue than protons do.
**A Proton Walks Into a Bar…**

A proton walks into a bar, sits down and orders a drink. After finishing the drink, the bartender says, “Would you like another drink?”

The proton says, “No, thanks.”

A few minutes later, the bartender approaches the proton again and says, “Are you sure you don’t want another drink?”

To which the proton says, “I’m positive.”

Punchline: Protons know when to stop!

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**Source:** [http://www.jokebuddha.com/Proton](http://www.jokebuddha.com/Proton)

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**Fig. 1.** Simple treatment plan for cranial-pediatric RT showing two distributions. (a) Sagittal view of 3D conformal treatment planning (red) with an isocenter at 100% of dose. (b) Tumor boost and (c) 4D conformal treatment planning (yellow). (d) Conventional treatment planning (blue) with an isocenter at 100% of dose. **Fig. 2.** Proton neutron vs. X-ray therapy: (a) Proton and (X-ray) therapy plan; (b) X-ray therapy plan. (c) Proton therapy plan.

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**Fig. 1.** A 14-year-old girl with supratentorial primitive neuroectodermal tumor; craniospinal irradiation prescribed to the cranial axis and spinal nerve roots only. (a) T1-weighted magnetic resonance imaging 1 week before radiation treatment; (b) Computed tomography—proton radiotherapy treatment plan; (c) T2-weighted magnetic resonance image showing hyperintense fully enhancing in presurgical aspect of spinal body. 1 month after completion of proton radiotherapy.
Roles of Radiation Therapy in GI cancers

- Preoperative (before surgery)
  - Improve local-regional control
  - Tumor downstaging
  - High risk T3+ N+

- Postoperative (after surgery)

- Definitive (unresectable)
  - Sterilize gross/microscopic residual disease in high-risk patients
  - T3+ N+

- Palliation (symptom control)
  - Pain
  - Bleeding
  - Obstruction
Pancreatic cancer

Pre-operative treatment
Adjuvant therapy
Unresectable disease

Reduction of dose to normal tissue

- Improved ability to reduce radiation dose to normal tissues
  - Small bowel
  - Stomach
  - Kidneys
  - Liver
  - Spinal cord

Reminder of Historical Acute G3+ chemoRT Toxicities

- Worst non-hematological ~60%
- Diarrhea 15-20%
- Nausea/vomiting 10-20%
- Anorexia 15%

Acute Toxicities: U Penn Preliminary Results

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Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity

- University of Florida data (2009-2012)
  - 22 patients treated to 50.4 – 59.4 CGE with concurrent capecitabine
  - No grade 3 toxicities
  - No treatment interruptions due to toxicity
  - Grade 2 toxicities – vomiting (n=3), diarrhea (n=2)
  - 2 patients with T4 disease rendered operable
  - R2 resection, NED at 10 mos post-op
  - One patient with complete pathologic response, NED at 9 months

Current proton studies for pancreatic cancer

- UF – neoadjuvant 50.4 GyE + xeloda for resectable disease
- UF – unresectable 59.4 GyE + xeloda
- UF – adjuvant 50.4-59.4 GyE + gemcitabine (300 mg/m2 weekly)
- MGH – neoadjuvant Folfirinox + short course protons for borderline resectable disease
- MGH – neoadjuvant xeloda + short course protons

Liver cancers

- Hepatocellular carcinoma
- Cholangiocarcinomas

Challenges in HCC and RT

2 life-threatening diseases: HCC and cirrhosis
- Multifocal disease (field cancerization)

Liver cancers

Challenges in HCC and RT

Liver and RT: Basic tenets

- Liver is sensitive to radiation
  - Whole liver tolerance ~30 Gy
  - Cirrhotics more sensitive
  - Radiation-induced liver disease (RILD) is life-threatening
  - Partial volume liver radiation tolerance is high
  - Radiation dose escalation improves clinical outcomes

Goals of therapy

- Improve local control
- Reduce toxicity
- Allow intensification of systemic therapy
Protons spare more normal liver

Wang et al. Med Dosim 2008

Study Pts Dose OS LC Notes
Kawashima JCO 2005 30 76 Gy (3.8 Gy x 20) BED 89 Gy 2-yr 66% 2-yr 96% Single CPA 8 yr OS 99%
Chiba CCR 2006 162 72 Gy (4.5 Gy x 16) BED 88 Gy 5-yr 24% 5-yr 87% Single CPA A 70%, CPA B 60%
Nakayama Cancer 2009 318 77 Gy (2.2 Gy x 35) BED 78 Gy 73 Gy (3.32 Gy x 22) BED 80 Gy 66 Gy (6.6 Gy x 10) BED 91 Gy 3-yr 65% 5-yr 45% 3-yr 95% 5-yr 88% 90% 5 cm
Fukumitsu IJROBP 2009 51 66 Gy (6.6 Gy x 10) BED 91 Gy 3-yr 50% 5-yr 39% 3-yr 95% 5-yr 88% 90% 9 cm
Sugahara IJROBP 2010 22 72.6 Gy (3.3 GY x 22) BED 82 Gy 2-yr 36% 2-yr 87% > 10 cm tumors
Bush Gastro 2004 76 63 Gy (4.2 Gy x 15) BED 76 Gy 2-yr 55% 2-yr 75% PROTONS PHOTONS (IMRT)

64 Gy

52 Gy

PROTONS

PHOTONS (IMRT)

Rectal cancer

Well established role in neoadjuvant therapy for locally advanced cancers

With chemotherapy, radiation is a curative modality for anal cancers
Short course pelvic radiotherapy

- Well established regimen 50 Gy x 5 shows improved local control over surgery alone
- Not adopted widely throughout the US due to concerns re: toxicity

Hypofractionated pre-operative proton therapy for rectal cancer

- Advantages
  - Reduced dose to small bowel, bladder → to reduce toxicity
  - Treatment completed within one week
  - Efficacy of this dose has already been demonstrated in phase III photon trials

Bone marrow-sparing pelvic proton therapy

- Background
  - 30-40% of adult bone marrow is contained within the pelvis
  - Hematopoietic cells are extremely sensitive to low doses of radiotherapy
  - Hematologic toxicity is common in patients receiving chemo-radiotherapy for pelvic cancer

Comparison proton, 3D, and IMRT plans

Protons and bone marrow sparing

Protons and small bowel sparing

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Abbreviations: SDCT, 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PBT, proton beam therapy.
Proton beam radiotherapy in Seattle

Proton Therapy Center Design

Inclined beam

Fixed beam

Proton Therapy Centers

SCCA Proton Therapy: Guiding Principles

- Increased use in diseases we do poorly treating now with conventional radiation and IMRT
- Scarce resource that should be used where there is the largest clinical impact
- Goal is to enroll majority, if not all, of our patients onto clinical trials

Eleven centers are operating in the U.S. and over 40 operate worldwide

SCCA Proton Therapy, A ProCure Center

A few facts

- 56,000 SF building
- Opened Q1 2013
- 4 treatment rooms
- 1 fixed beam
- 2 incline beam rooms
- 1 gantry room
- 18A proton beam equipment
- $150 Million Investment
Summary

• Protons allow us to control where radiation stops in tissue
• May reduce risk of second malignancies
• Reduces toxicity
• Allows intensification of therapy (either chemotherapy or radiation)
• Protons are very resource intensive
• GI malignancies are an active area of exploration

Thank You

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