The Physical and Biological Basis of Radiation Therapy

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Wilhelm Conrad Roëntgen

Discovered X rays in 1895
X rays were immediately big news at Columbia

“The College of Physicians and Surgeons is using x-rays to reflect diagrams directly on to the students’ brains, making a more enduring impression than the normal method of learning”

*New York Morning Journal, 1896*

By 1899 X rays were being used for cancer therapy

A 1899   B 1929
Who gets radiotherapy?

Half of all cancer patients get radiotherapy
Who gets radiotherapy?

Half of all RT patients are treated with curative intent.

Who gets radiotherapy?

Half of all RT patients treated with curative intent are cured.
RT has both a physical and a biological basis

The goal is always to produce as much cell killing as possible in the tumor, while minimizing damage to normal tissue.

Physical Basis of Radiotherapy

- Aim beam at tumor
- Shape beam to conform to the tumor
- Minimize dose to normal tissue
External-beam radiotherapy: 1951

Higher energy beams and aiming at the tumor from more directions, made for better dose distributions.
IMRT (intensity modulated radiation therapy)

Continuously changing multi-leaf collimator

The CyberKnife, an x-ray machine on the end of a robotic arm
The bottom line in 2006 is that far more normal-tissue dose sparing can be achieved than was previously possible.
By late 1903, the first treatment of cervical cancer with radium was reported from New York.

Radioactive seeds are increasingly used for treating prostate cancer.
The Three R's of Radiotherapy

- Repair
- Reoxygenation
- Repopulation

Repair of DNA damage
Radiation-induced DNA Damage

1. Intact DNA
2. Break in a single strand
3. Two strand breaks far apart
4. 2 breaks close together opposite

Taking advantage of DNA damage repair

- DNA repair is different for tumors (proliferating tissue) compared with late-responding normal tissues (slowly proliferating tissue)
- Dividing the treatment into many fractions takes advantage of this, allowing for more repair in late-responding normal tissue than in tumors
The significance of oxygenation:

Hypoxic cells have very poor responses to radiotherapy.

Solution is fractionation:

Allows reoxygenation between treatments.
**Accelerated Repopulation**

As the tumor shrinks, the surviving tumor cells proliferate at an accelerated rate.

**Loss of tumor control as a result of increasing overall treatment time**

- 2% per day for head and neck tumors
- 1% per day for cervix, bladder cancers
Biological Basis of Radiotherapy

- Exploit biological differences between tumor and normal tissues
- Minimize effects of hypoxic cells
- Fight accelerated repopulation

From a biological perspective:

Must divide radiotherapy treatment into many separate fractions

- To overcome hypoxia
- For differential response of tumor control and late side effects
From a biological perspective:

- **Must keep the treatment short**
  - To counteract accelerated population

- **Must prolong the treatment**
  - To limit early side effects

The Physical and Biological Bases of Radiation Therapy

- 1.4 million malignant cancers / yr in the US
- Half of them treated with radiotherapy
- Radiation therapy uses both physics biology to maximize the differential between tumor control and side effects
Clinical Principles of Radiation Therapy

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Columbia University Medical Center

Targeted Therapy in Oncology

- Surgical Oncology
  - Minimal invasive techniques
- Medical Oncology
  - Tumor specific biological targets
- Radiation Oncology
  - IMRT
  - Brachytherapy
  - Protons
  - IGRT
TOPICS

• Primary Radiation Therapy (Radiosurgery)
• Combing RT and Surgery
• Chemo/RT
  • Ca Esophagus
  • EGFR, monoclonal antibody cetuximab + RT for H&N Ca
• 3D-CRT Treatment of Localized CaP ± AD
• IGRT

Clinical Principles of Radiation Therapy

Primary Radiation Therapy
Combining Radiation Therapy and Surgery

Pre-operative vs Post-Operative Radiation Therapy
Pre-Operative vs. Post-Operative Radiation Therapy

Pre-operative irradiation may:

- Increase tumor's resectability
- Eliminate potential seeding of tumor during surgery
- Destroy microscopic foci of tumor that may extend beyond the surgical margins of resection
- Treat a relatively well-oxygenated tumor that may be more radiosensitive
- Allow a smaller treatment field because the operative bed has not been contaminated
- Decrease complications that may be associated with post-operative irradiation

Pre-Operative vs. Post-Operative Radiation Therapy

Disadvantages of pre-operative irradiation include:

- Inability to select patients on the basis of anatomical extent of disease
- Inability to tailor the irradiation to high-risk sites following the surgical procedure
- Delay primary treatment, which is surgery in most cases
- Increase incidence of post-operative complications associated primarily with wound healing
- Limitation of radiation total dose by the planned surgery
- Pathological downstaging, which may influence selection of adjuvant therapy
Pre-Operative vs. Post-Operative Radiation Therapy

Advantages of post-operative irradiation include:

- Extent of disease is known at the time of irradiation, and treatment can be individually tailored
- Operative margins may be more easily defined
- Operative wound healing will be intact and the likelihood of surgical complications less
- Tenuous surgical procedures such as GI anastomoses and ileal conduits can be done in a nonirradiated field
- Potential for unnecessary irradiation with some patients is reduced

Pre-Operative vs. Post-Operative Radiation Therapy

Disadvantages of post-operative irradiation include:

- Delivery of necessary irradiation may be delayed by poor wound healing or by surgical complications
- Tumor may be poorly oxygenated following disruption of blood supply and less sensitive to external beam irradiation
- Irradiation would have no effect on dissemination of tumor at the time of surgical manipulation
- Volume of normal tissue requiring irradiation may be greater after surgery
- Operative procedure may fix certain critical organs in the irradiated field, resulting in increased risk of injury to such structures as the small bowel
Clinical Principles of Radiation Therapy

Radiation Therapy and Chemotherapy

**MODES THROUGH WHICH COADMINISTRATION OF CYTOTOXIC AGENTS (INCLUDING RADIATION) MAY RESULT IN AN INCREASED THERAPEUTIC RATION**


- Enhancement of the tumor response compared to that of normal tissue
- Normal-tissue toxicity independence
- Spatial cooperation (where disease at one anatomical site that is insensitive to one agent is controlled by the second agent)
- Normal tissue protection without concomitant protection of tumor cells
STRATEGY OF RADIOSENSITIZERS

Tumor control probability

Sensitized cure

Cure

Normal tissue damage ± sensitizer

Dose (Gy)

POTENTIAL ADVANTAGES AND DISADVANTAGES OF CHEMORADIATION

Advantages:

- Concurrent treatment may start soon after surgery
- Possible supra-additive effect on local tumor control
- Avoids treatment break between chemotherapy cycles associated with "sandwich" approach
- Shortens overall length of treatment program
POTENTIAL ADVANTAGES AND DISADVANTAGES OF CHEMORADIATION (cont)

Disadvantages:

- Greater acute myelosuppression
- Increased acute skin reaction
- Acute side effects may result in delays or dose reductions of chemotherapy
- Increase risk of subacute side effects, such as pneumonitis
- Increase risk of chronic side effects, such as cardiotoxicity
- Worsened cosmetic outcome

Combined Chemotherapy and Radiotherapy Compared with Radiotherapy Alone in Patients with Cancer of the Esophagus

RTOG
NEJM 326:1593-1598, 1992
Combined Chemotherapy and Radiotherapy Compared with Radiotherapy Alone in Patients with Cancer of the Esophagus

• Combination group: 4 cycles of combined 5-FU (1000 mg/m², for four days) and cisplatin (75 mg/m², day 1) plus RT (50 Gy)

• Radiation only group: 64 Gy

Combined Chemotherapy and Radiotherapy Compared with Radiotherapy Alone in Patients with Cancer of the Esophagus

Side Effects

Combination treatment group
• 1 treatment related death
• more severe side effects (44% vs. 25%)
• life-threatening side effects (20% vs. 3%)
RT plus Cetuximab for Squamous-Cell Carcinoma of the Head & Neck
Bonner et al., NEJM 2006, 354:567

- Multinational, randomized clinical trial comparing RT alone (213 pts) with RT plus cetuximab (211 pts)
- Stage III or IV nonmetastatic SCC of oropharynx, hypopharynx or larynx
- RT up to 72 Gy
- Cetuximab iv 400 mg M² followed by weekly infusions of 250 mg M²
Treatment of Localized Prostate Cancer with Radiation Therapy

Combined Modality Treatment with AD in Selected Patients

Organ Confined Prostate Cancer

Treatment Options
- Radiation therapy ± hormonal intervention
- Surgery ± hormonal intervention
- Hormonal intervention only
- Observation
- Other local therapies
Organ Confined Prostate Cancer

Radiation Therapy

- 3D-conformal radiation therapy (3D-CRT)
- Brachytherapy
- Combination of 3D conformal radiation therapy and brachytherapy
Columbia Biologic Classification of Clinically Localized Prostate Cancer

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6-Month AD + 3D-CRT vs RT Alone for Patients Localized CaP


- 206 patients randomized to 3D-CRT (70 Gy) alone (n=104) or in combination with 6 months AD (n=102)
- Eligible patients included those with PSA ≥ 10 ng/mL, a Gleason score ≥ 7, or radiographic evidence of extracapsular disease
# 6-Month AD + 3D-CRT vs RT Alone for Patients Localized CaP

Harvard, JAMA 292:821-827, 2004

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# Clinical Principles of Radiation Therapy

*Image-Guided Radiation Therapy (IGRT)*
IGRT

• Medical professional teams working together

• Availability of new imaging modalities of tumors and normal tissues (CT/PET, MRI, MRS, USTT)
  • Anatomy now being fused with biologic function.

• Adaptive Radiotherapy (gating, organ motion, use of EPIDs, etc).

• CT/MRI virtual simulation

IGRT Technologies

• CyberKnife (linear accelerator on robotic arm)

• Trilogy (linear accelerator with minimultileaf collimators and imaging arms)

• TomoTherapy (CT-like unit with linear accelerator)

• Protons

• Carbon ions
In-Room KV X-rays: Prostate Markers
BrainLab Exactrac™

Marker Seeds
Marker Seeds

Investigational Device
Not For Sale

Beacon™ Transponder

- Wireless 15 G, permanent implant
- RF signal detected externally
- Refresh rate: 10 Hz
- No X-ray (no dose)
- Continuous target localization, registration & tracking
8 Minutes of Continuous Calypso Monitoring

MD-10

Target Position (cm)

Time (sec)

Lateral

MD-05

Target Position (cm)

Time (sec)

Lateral

Longitudinal

Vertical
Cone Beam KV CT

Elekta Synergy
- Same Gantry
- Coupled to delivery device
- Volume acquisition
- 5-10 min for image guidance
- 1-2 cGy per scan

Varian Trilogy

CYBERKNIFE

Targeting System

X-ray sources
- Synchrony™ camera
- Manipulator
- Linear accelerator
- Robotic Delivery System
- Treatment couch
- Image detectors
MRS Detection of Prostate Cancer

John Kurhanewicz, Ph.D.
Magnetic Resonance Science Center, Department of Radiology
University of California San Francisco
Region of Interest (ROI) and Spectrum (basis for characterizing tissue)

A. 3-D rendering of a prostate with a TZ³ protruding tumor and PZ tumor. View from the base of the grand.

B. 3-D rendering of a prostate with cancer suspicious regions predominantly in the PZ.
Dose Sculpting & Imaging

• New imaging modalities combined with IMRT (or brachytherapy) open the way to modulating dose within diseased organs

• Success is dependent not only to the ability of IMRT (or brachytherapy) to modulate dose but also on the quality of imaging modalities
Clinical Principles of Radiation Therapy

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