Principles of Radiation Therapy

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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

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

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
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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

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
EGFR/HER1: A Key Factor in Tumorigenesis

Cetuximab + RT: Enhances Antitumor Activity In Vitro

- As cells progress through the cell cycle, their sensitivity to ionizing radiation fluctuates. During S phase (DNA synthesis), resistance to radiation is greatest
  - *In vitro* studies have shown that Cetuximab causes the arrest and accumulation of cells in the G₁ phase, when radioresistance is low
  - Ionizing radiation induces the arrest of cells in the G₂ phase
P = 0.005

No. at Risk
Radiotherapy 213 122 80 51 30 10
Radiotherapy plus cetuximab 211 144 101 66 35 9

P = 0.03

No. at Risk
Radiotherapy 213 162 122 97 73 47 22
Radiotherapy plus cetuximab 211 177 136 116 98 61 24
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Treatment of Localized Prostate Cancer with Radiation Therapy

Combined Modality Treatment with AD
In Selected Patients
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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Columbia University, Urology 51:265-270, 1998

6-Month AD + 3D-CRT vs RT Alone for Patients Localized CaP
Harvard, JAMA 292:821-827, 2004

• 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

<table>
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<th>% 5-Year Overall Survival</th>
<th>% 5-Year Survival Without Progression</th>
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IGRT
IGRT

**New paradigms and other considerations**

- Medical professional teams working together
- Availability of new imaging modalities of tumors and normal tissues (CT/PET, MRI, MRS, USTT, etc). Anatomy now being fused with biologic function.
- Adaptive Radiotherapy (gating, organ motion, use of EPIDs, etc).
- CT/MRI virtual simulation

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IGRT

- Respiratory motion of a lung tumor (axial view)
IGRT

- Respiratory motion of a lung tumor (sagittal view)

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
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
- Robotic Delivery System
- Linear accelerator
- Image detectors
- Treatment couch
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)


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
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THANK YOU