Principles of Radiation Oncology

Michael Underbrink, MD
Faculty Advisor: Anna Pou, MD
The University of Texas Medical Branch
Department of Otolaryngology
Grand Rounds Presentation
December 3, 2002
Introduction

- Increasing use for head and neck cancer
- Combined or as single modality
- Outline basic principles, radiobiology
- General treatment approach
- Common complications
Radiation Physics

- **Basis** – ionizing particles interact with cellular molecules
- **Relies on transfer of energy created by secondary charged particles (usually electrons)**
- **Break chemical bonds**
- **External beam vs. Brachytherapy**
- **Radiant energy is discrete yet random**
External Beam Irradiation

- Dual-energy linear accelerators generate:
  - Low energy megavoltage x-rays (4-6 MeV)
  - High energy x-rays (15-20 MeV)
  - Photon energy

- Particle Radiation (electrons, protons, neutrons)

- Photon therapy advantages
  - Skin sparing, penetration, beam uniformity

- Head and Neck sites – 4-6 MeV x-ray or Co60 gamma ray radiation
External Beam Irradiation

**Figure 31-1** Central axis percent depth dose curves of x-rays and γ-rays (A) and electron beams (B) of different energies and those of 200-MeV proton beams with or without modulation (C). The x-ray beams fall off exponentially after the initial buildup, whereas the dose for proton beam rises slowly to reach the Bragg peak (BP) where the protons stop. When the proton is modulated, the Bragg peak spreads out (SOBP) but the superficial dose also increases. The advantage of the proton beam is the absence of dose beyond the Bragg peak and lower surface dose. Electrons have beam characteristics similar to those of protons except that the dose fall-off is not as sharp owing to the light mass of electron, and the surface dose is relatively high (no skin-sparing effect).
Brachytherapy

- Radioactive source in direct contact with tumor
  - Interstitial implants, intracavitary implants or surface molds
- Greater deliverable dose
- Continuous low dose rate
- Advantage for hypoxic or slow proliferators
- Shorter treatment times
Brachytherapy

• Limitations
  – Tumor must be accessible
  – Well-demarcated
  – Cannot be only modality for tumors with high risk of regional lymph node metastasis
# Brachytherapy

## Table 101.1. Physical Characteristics of Commonly Used Brachytherapy Sources

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>X or Gamma ray Energy (keV)</th>
<th>Physical Configuration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesium 137</td>
<td>30 y</td>
<td>662</td>
<td>Tubes, needles</td>
<td>Relatively inexpensive</td>
<td>Relatively large sources; limited sizes and strengths</td>
</tr>
<tr>
<td>Gold 198</td>
<td>2.7 d</td>
<td>412</td>
<td>Seeds</td>
<td>Small size; higher dose rate; relatively inexpensive</td>
<td>Not usually afterloaded</td>
</tr>
<tr>
<td>Iodine 125</td>
<td>60 d</td>
<td>27–35</td>
<td>Seeds</td>
<td>Small size; less exposure to personnel</td>
<td>Low dose rate</td>
</tr>
<tr>
<td>Palladium 103</td>
<td>17 d</td>
<td>20–23</td>
<td>Seeds</td>
<td>Small size; higher dose rate; less exposure to personnel</td>
<td>Expensive</td>
</tr>
<tr>
<td>Iridium 192</td>
<td>74 d</td>
<td>136–1,060</td>
<td>Wire, seeds, catheters (afterloading)</td>
<td>Wide variety of source strengths and sizes; usually afterloaded</td>
<td>—</td>
</tr>
<tr>
<td>Radium 226</td>
<td>1,620 y</td>
<td>47–2,440</td>
<td>Tubes, needles</td>
<td>Relatively large sources; no appreciable decay with time</td>
<td>Limited sizes and strengths; potential for leakage and contamination</td>
</tr>
</tbody>
</table>
Radiobiology

- Ionizing radiation ejects an electron from a target molecule
- Distributed randomly within cell
- Double-strand DNA breaks – lethal
- Cell death: no longer able to undergo unlimited cell division
- Direct vs. Indirect injury (free radicals – O\textsubscript{2})
- Inadequate cellular repair mechanisms implied
Radiobiology

• **Random cell death**
  – Deposition of energy & injury is random event
  – Same proportion of cells is damaged per dose
  – 100 to 10 cell reduction = $10^6$ to $10^5$ cell reduction
  – Larger tumors require more radiation
  – $10^5$ cells = nonpalpable
  – Applies to normal tissue also

• **Therapeutic advantage** – 4 R’s of radiobiology
4 R’s of radiation biology

- **Repair** of cellular damage
- **Reoxygenation** of the tumor
- **Redistribution** within the cell cycle
- **Repopulation** of cells
Repair of sublethal injury

- Sublethal injury – cells exposed to sparse ionization fields, can be repaired
- Killing requires greater total dose when given in several fractions
- Most tissue repair in 3 hours, up to 24 hours
- Allows repair of injured normal tissue, potential therapeutic advantage over tumor cells
- Radioresistance – melanoma?
Reoxygenation

- Oxygen stabilizes free radicals
- Hypoxic cells require more radiation to kill
- Hypoxic tumor areas
  - Temporary vessel constriction from mass
  - Outgrow blood supply, capillary collapse
- Tumor shrinkage decreases hypoxic areas
- Reinforces fractionated dosing
- Hypoxic cell radiosensitizers, selective chemo
Reoxygenation
Redistribution

- Cell cycle position sensitive cells
- S phase – radioresistant
- $G_2$ phase delay = increased radioresistance
- RAD9 gene mutation – radiosensitive yeast
- H-ras and c-myc oncogenes - $G_2$ delay
- Fractionated XRT redistributes cells
- Rapid cycling cells more sensitive (mucosa, skin)
- Slow cyclers (connective tissue, brain) spared
Redistribution
Repopulation

- Increased regeneration of surviving fraction
- Rapidly proliferating tumors regenerate faster
- Determines length and timing of therapy course
- Regeneration (tumor) vs. Recuperation (normal)
- Reason for accelerated treatment schedules
- Reason against:
  - Treatment delay
  - Protracted XRT, split course XRT (designed delay)
Repopulation

**FIGURE 101.8.** Tumor growth curves for a rapidly proliferating tumor and a slowly proliferating tumor. The initial growth of a tumor is exponential. However, growth begins to plateau as the tumor enlarges, presumably because of inadequate blood supply and a lack of nutrients. When the tumor cell population is reduced, as by surgery or irradiation, the malignant cells respond with accelerated repopulation. The difference between the growth rate of unperturbed tumor (AB) and the more rapid growth rate after surgery or irradiation (ABBB) is evident. Accelerated regrowth is a greater problem with rapidly proliferating tumors than with slowly proliferating tumors.
Dose-Response Relations

• Control probability variables
  – Tumor size
  – XRT dose

• Favorable response curves
  – Small, well-vascularized tumors
  – Homogeneous tumors

• Unfavorable response curves
  – Large, bulky tumors (hypoxia)
  – Heterogeneous, variable cell numbers

• Normal tissue injury risk increases with XRT dose (size of tumor)
Dose-Response Relations
Fractionation

FIGURE 31–5 Survival curves of fractionated radiation delivered in equal doses per fraction separated by time interval, allowing complete repair from SLD to elapse. The curves become exponential as a function of radiation dose. The slope of each curve is defined by the respective “effective” $D_{0e}$ [$D_{Q(eff)}$] for a particular fraction size. The $D_{0(eff)}$ can never exceed $D_{0}$ because this denotes single-hit killing that results from irreparable damage.
Fractionation Schedules

• Conventional
  – 1.8 to 2.0 Gy given 5 times/week
  – Total of 6 to 8 weeks
  – Effort to minimize late complications

• Accelerated fractionation
  – 1.8 to 2.0 Gy given bid/tid
  – Similar total dose (less treatment time)
  – Minimize tumor repopulation (increase local control)
  – Tolerable acute complications (increased)
Fractionation Schedules

• Hyperfractionation
  – 1.0 to 1.2 Gy bid/tid, 5 times/week
  – Similar total treatment time (increased total dose)
  – Increases total dose
  – Potentially increases local control
  – Same rates of late complications
  – Increased acute reactions
Treatment Principles

- Size and location of primary
- Presence/absence and extent/incidence of regional or distant metastasis
- General condition of patient
- Early stage cancers
  - Surgery alone = XRT alone
  - Treatment choice depends on functional deficits
- Late stage – usually combination of treatments
Treatment Principles

- Surgical salvage of primary radiation failures is better than radiation salvage of surgical failure
- Explains rationale behind organ preservation strategies
- XRT tumor cell killing is exponential function
  - Dose required for tumor control is proportional to the logarithm of the number of viable cells in the tumor
Shrinking field technique

- **Initial dose = 45 to 50 Gy (4.5 to 5.0 weeks)**
  - Given through large portals
  - Covers areas of possible regional metastasis and primary

- **Second dose = 15 to 25 Gy (1.5 to 2.5 weeks)**
  - Boost field (gross tumor and small margin)
  - Total dose of 60 to 75 Gy in 6 to 7.5 weeks

- **Boost dose = 10 to 15 Gy**
  - Massive tumors
  - Second field reduction at 60 to 65 Gy
  - Total of 7 to 8 weeks
Combined Modalities

- Surgery and XRT complement each other
- Surgery – removes gross tumor (bulky tumors are more difficult to control with XRT)
- XRT – effective for microscopic disease, better with exophytic tumors than ulcerative ones (Surgical failures may leave subclinical disease)
- Combining treatments counteracts limitations
- Pre or Post-operative XRT
Preoperative XRT

• Advantages
  – Unresectable lesions may become resectable
  – Extent of surgical resection diminished
  – Smaller treatment portals
  – Microscopic disease more radiosensitive (blood supply)
  – Decreased risk of distant metastasis from surgical manipulation?

• Disadvantages
  – Decreased wound healing
  – Decreased safe dose (45 Gy in 4.5 weeks eradicates subclinical disease in 85% to 90% of patients)
Postoperative XRT

• Advantages
  – Better surgical staging
  – Greater dose can be given safely (60 to 65 Gy in 6 to 7 weeks)
  – Total dose can be based on residual tumor burden
  – Surgical resection is easier
  – Tissue heals better

• Disadvantages
  – Distant metastasis by manipulation?
  – Delay in postoperative treatment if healing problems (poorer results if delayed more than 6 weeks)
Complications

- Acute Tissue Reactions
- Late Tissue Reactions
Acute Toxicity

- Time onset depends on cell cycling time
- Mucosal reactions – 2\textsuperscript{nd} week of XRT
- Skin reactions – 5\textsuperscript{th} week
- Generally subside several weeks after completion of treatment
- RTOG – acute toxicity <90 days from start of treatment (epithelial surfaces generally heal within 20 to 40 days from stoppage of treatment)
Acute Toxicity

- Mucositis – intensity-limiting side effect for aggressive schedules
- Accelerated fractionation – increase acute toxicities
- Conventional fractionation conservatively emphasized maximum tolerated dose is limited by late not acute tissue injury
Late Toxicity

- Injury tends to be permanent
- Cells with low turnover (fibroblasts, neurons)
- Develop within months to years
- Xerostomia, dental caries, fibrosis, soft-tissue necrosis, nerve tissue damage
- Most common - xerostomia
**Late Toxicity**

*FIGURE 31–7* Isoeffect curves (total doses inducing an equal biologic effect vs dose per fraction) for acutely (*dashed lines*) and late-responding (*solid lines*) tissues. The curves for late effects are steeper than those for acute reactions, indicating that as the dose per fraction is reduced, higher total dose of radiation is needed to inflict the same magnitude of damage.73
Late Toxicity

- **Xerostomia**
  - Injury to serous acinar cells
  - May have partial recovery
  - Results in dental caries (in or outside of fields)

- **Soft tissue necrosis**
  - Mucosal ulceration, damage to vascular connective tissue
  - Can result in osteo-/chondroradionecrosis
Late Toxicity

FIGURE 29-14  Osteoradionecrosis in the posterior mandible is secondary to trauma.
Late Toxicity

- **Fibrosis**
  - Serious problem, total dose limiting factor
  - Woody skin texture – most severe
  - Large daily fractions increase risk

- **Ocular** – cataracts, optic neuropathy, retinopathy

- **Otologic** – serous otitis media (nasopharynx, SNHL (ear treatments))
Late Toxicity

FIGURE 29-15  Radiation-induced trismus is shown.
Late Toxicity

- **Central Nervous System**
  - Devastating to patients
  - Myelopathy (30 Gy in 25 fractions)
    - Electric shock from cervical spine flexion (Lhermitte sign)
  - Transverse myelitis (50 to 60 Gy)
  - Somnolence syndrome (months after therapy)
    - Lethargy, nausea, headache, CN palsies, ataxia
    - Self-limiting, transient
  - Brain necrosis (65 to 70 Gy) – permanent
Conclusions

- XRT key role in treatment of H&N cancer
- Fundamentals of radiation physics and radiobiology explain rationale behind treatment schedules and complications
- Basic knowledge important with regard to patient counseling