PRINCIPLES OF RADIATION ONCOLOGY

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**HISTORY**

- X-rays discovered in 1895
- Becquerel’s accidental experiment showed the first radiobiological effects of x-rays
- Experimentation of ram testicles revealed radiosensitivity of different tissues
- Higher energy units available in 1950s and advent of linear accelerators
Basis of radiation for therapy

- Electromagnetic radiations release energy indirectly to cause cellular damage.
- X-rays and Gamma rays are similar in action; their production is different.
- X-rays are produced extranuclearly.
- Gamma rays produced intranuclearly.
Production of radiation to cause effect

- Depth of irradiation depends on radiation beam
- Lower energy beams affect skin
- Higher energy beams spares skin
- Difference between Cobalt-60 and lower energy linear accelerators involves beam shape
Fig. 1-2. Percentage depth-dose curves for a variety of radiations commonly used in radiation therapy. The inset shows the pattern of absorption at shallow depths and provides a rationale for the skin-sparing effect.

Table 1-1. Teletherapy Sources

<table>
<thead>
<tr>
<th>Unit</th>
<th>Mean Energy (MeV)</th>
<th>Photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>150-440 kVp x-ray</td>
<td>0.06-0.14</td>
<td></td>
</tr>
<tr>
<td>$^{137}$Cs teletherapy</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>$^{60}$Co teletherapy</td>
<td>1.25</td>
<td></td>
</tr>
<tr>
<td>4 MV linear accelerator</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>6 MV linear accelerator</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>20-24 MV betatron and linear accelerator</td>
<td>6.2-7.0</td>
<td></td>
</tr>
</tbody>
</table>

Table 1-2. Brachytherapy Sources

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-Life</th>
<th>Effective Energy (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{226}$Ra</td>
<td>1620 years</td>
<td>1.2</td>
</tr>
<tr>
<td>$^{137}$Cs</td>
<td>30 years</td>
<td>0.66</td>
</tr>
<tr>
<td>$^{198}$Au</td>
<td>2.7 days</td>
<td>0.41</td>
</tr>
<tr>
<td>$^{192}$Ir</td>
<td>74 days</td>
<td>0.34</td>
</tr>
<tr>
<td>$^{125}$I</td>
<td>60 days</td>
<td>0.027</td>
</tr>
</tbody>
</table>

MeV, million electron volts.
Fig. 5-14, cont’d. D, Same patient 8 months after treatment. He remained well over 5 years.
Radiation Dose Quantification

- Rad has generally been replaced by Gray
- Measurement of dose is difficult directly
- Absorbed dose is calculated based on indirect measurements of ionization of air
- Pattern of energy deposition varies with types of particles causing cellular disruption
Fig. 1-4. When a population of cells is irradiated with 10 rad of x-rays, a number of charged particle tracks traverse every cell. By contrast, in the case of neutrons, only a small proportion of the cells are traversed by a charged particle track. Consequently, when the x-ray dose is increased, the average energy deposited per cell is increased. When the neutron dose is increased, the number of cells in which energy is deposited is increased. This is a fundamental difference.
Fig. 1-26. The survival curve for x-rays is characterized by a broad initial shoulder, while for neutrons the survival curve has little or no shoulder. Consequently the relative biologic effectiveness (RBE) gets larger as the dose gets smaller. When a dose is fractionated, the RBE is larger for a given level of cell killing than if the dose is given in a single exposure, since the large shoulder of the x-ray dose-response curve is repeated each time.
Effects on Tumors

- Both malignant cells and normal cells respond similarly to radiation
- Both undergo repair of sublethal damage
- Both cell types are more sensitive during the mitotic phase
- Only malignant cells have areas of hypoxia - reason for fractionation
FIG. 99-6. Hypoxic cells in a lung cancer. The area of necrosis is 160 μm from the nearest capillary, which causes the hypoxic cells at the edge of necrosis to be relatively radioresistant.
Systemic Effects

- Data exists from accidental human exposure and animal research
- A value often used is LD50 which is the lethal dose for 50% of the population sample
- Deaths due to total body exposure
- When TBI used before bone marrow transplant, interstitial pneumonitis is the limiting factor
Systemic effects continued

- Effects on immune reactions vary
- Depressions generally occur only when large tumors are irradiated or large surface areas
- Nausea and vomiting secondary to irradiation or disease processes
- Nausea that presents later during treatment may be secondary to underlying disease process
Radiobiology

- Fractionation
- Reassortment of cells
- Repair of sublethal damage
- Accelerated repopulation
Fractionation

- Single prolonged dose has profound effects on normal tissues
- Studies on spermatogenesis of rams
- Reason for fractionation - allows tumor cells to reassort into the mitotic phase
- Reduces hypoxia while sparing normal tissues
Reassortment

- Cells more radiosensitive in mitosis or late in G2
- Survival curve is steep in these stages
- Fractionation permits cells to reassort themselves into more sensitive phases of the cell cycle to allow better killing
Sublethal Damage Repair

- Molecular basis not understood
- Defined as increase in survival when a dose of radiation is split
- This feature is ubiquitous among cells
- Because of ability to repair damage quickly, melanomas have been thought of as “relatively radioresistant”
Accelerated Repopulation

- Tumor cells respond quickly after irradiation with increased rates of cell doubling
Rationale for fractionation

- Reassortment allows for better cell killing
- Repair of sublethal damage should be minimized
- Reoxygenation allows for better cell killing
- Hyperfractionation used to minimize the late effects of irradiation while increasing dose and tumor control
Fig. 1-14. A, Increase in cell survival observed when a dose of radiation is delivered in 2 fractions separated by a time interval adequate for repair of sublethal damage. When the dose is split into 2 fractions, the shoulder must be expressed each time. B, The fraction of cells surviving a split dose increases as the time interval between the 2 dose fractions increases. As the time interval increases from zero to 2 hours, the increase in survival is due to the repair of sublethal damage. In cells with a long cell cycle, or that are out of cycle, there is no further increase in cell survival by separating the dose by more than 2 or 3 hours.
Fig. 1-19. Cells irradiated in the presence of molecular oxygen are more sensitive to killing by x-rays than cells that are hypoxic, i.e., deficient in oxygen. The ratio of doses in the absence of oxygen and the presence of oxygen required to produce the same level of biologic damage is known as the oxygen enhancement ratio (OER). At high doses, it has a value of about 3. There is some evidence that it has a smaller value, close to 2, at doses below 2 Gy.
Fig. 1-15. The dose rate effect. For sparsely ionizing radiations such as x-rays and gamma rays, the biologic effectiveness of a given radiation dose decreases as the dose rate is lowered. This occurs when the exposure time becomes comparable to, or longer than, the halftime of repair of sublethal damage, so that sublethal damage is repaired during the protracted exposure. As the dose rate is progressively reduced, the slope of the survival curve gets shallower, i.e., the final slope (Do) increases, and the shoulder of the survival curve disappears. The dose-response curve then approximates to an exponential function of dose.
Tumor volume and control by dose of irradiation

- Difficult to extrapolate data
- Assumptions must be made:
  - number of cells proportional to volume
  - hypoxia does not vary with tumor size
- 60 Gy leads to depopulation of 10,000,000,000 or regression of a 2 cm mass in 90% of patients
Table 1-4. Interrelationship of Biologic Dose, Tumor Size, and Control by Irradiation

<table>
<thead>
<tr>
<th>Total Dose (cGy)*</th>
<th>Histology</th>
<th>Size</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000</td>
<td>Squamous</td>
<td>Subclinical</td>
<td>95+</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma</td>
<td>(&lt; 10^6 cells)</td>
<td></td>
</tr>
<tr>
<td>6000</td>
<td>Squamous</td>
<td>&lt; 2 cm</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 4 cm</td>
<td>50</td>
</tr>
<tr>
<td>6500</td>
<td>Squamous</td>
<td>2-4 cm</td>
<td>70</td>
</tr>
<tr>
<td>7000</td>
<td>Squamous</td>
<td>2-4 cm</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma</td>
<td>&gt; 4 cm</td>
<td>60</td>
</tr>
<tr>
<td>7500+</td>
<td>Squamous</td>
<td>&gt; 4 cm</td>
<td>90</td>
</tr>
</tbody>
</table>

Data compiled from Fletcher and Shukovsky, Perez and associates, Barker and Fletcher, Shukovsky and Fletcher.
*Approximation based on a minimum tumor dose of 200 cGy per fraction and 5 fractions per week.
Combining radiation therapy and surgery

- Improved local regional control with combined modality
- Central hypoxic area of tumor is relatively radioresistant while peripheral fingers of tumor are not accessible surgically
Preoperative Irradiation

- Unresectable lesions made resectable
- Treatment portals for radiation are smaller
- Microscopic disease is more sensitive preoperatively
- Wound healing is difficult
- A smaller dose can be given
- With positive margins, it is difficult to add significant postop meaningful dose
Postoperative Irradiation

- Anatomic extent of tumor determined more accurately
- Greater dose can be given
- Theoretical disadvantage of tumor spillage by surgical procedure
- Positive and close margins indicate increased tumor burden and increased radiation dose
Oral Cavity and Oropharynx

- SCCA is most common histopathologic type
- Primary radiation or surgery depends on patient, surgeon, radiotherapist and institution
- Generally oropharyngeal neoplasms are treated with irradiation while oral cavity neoplasms are treated with surgery
Oral Cavity and Oropharyngeal Neoplasms

- T1 and small T2 lesions may be treated effectively with either irradiation or surgery.
- Larger tumors require combined modality.
- Smaller lesions that are relatively inaccessible surgically are best tailored for primary irradiation.
Indications for postop irradiation to the primary

- Larger T2 lesions or bigger
- Close or positive margins
- Perineural Invasion
- Patients with initially positive margins who undergo reexcision and have negative margins
Indications for treatment of neck postoperatively

- Poor prognostic factors
- Thickness of lesion > 2 mm
- More than 1 positive node or ecs present
- Contralateral prophylactic neck dissection not indicated
- Bad histopathology
- Optimal oral hygiene and pretreatment dental care
Radiation Techniques

- 10 days after dental extraction to allow healing
- Opposing lateral fields (reduces risk of orn)
- Bite block and Field of Treatment
- Posterior neck treatment should spare spinal cord at 45 Gy

Doses given

Shrinking Field Technique
Fig. 5-12. Standard radiation fields used for extensive tumors in the lower aspect of the oral cavity. In early well-differentiated tumors, such as in verrucous carcinomas, the fields to the primary tumor can be reduced in size and shaped accordingly. In such cases, the lower neck field can be omitted in the absence of palpable neck nodes. Spinal cord protection should be introduced after a dose of 4600 cGy (daily fractions of 180 to 200 cGy) has been delivered to this structure.
Fig. 5-13. Standard radiation fields for carcinomas in the oropharynx. Irradiation can be accomplished with blocking or with tailored Cerrobend blocks. If the tumor extends significantly into the oral cavity, the anterior coverage of the field should be more than shown. When the posterior pharyngeal wall is involved down into the hypopharynx, the midline protection should be omitted during most of the irradiation and the fields should extend into the nasopharynx. However when no midline blocking is possible, the posterior lower 1 cm edge of both lateral beams should be shielded to minimize the risk of overlap (caused by divergence) at the level of the spinal cord. Spinal cord protection should be introduced after a dose of 4500 cGy (daily fractions of 180 to 200 cGy) has been delivered to this structure.
Sequelae of Treatment

- Acute and late effects
- Mucositis
- Dysphagia
- Osteoradionecrosis increases with irradiated volume and increased dose and proximity of dose to mandible
- Lhermitte’s syndrome and transverse myelitis
Fig. 5-24. A, Massive mandibular necrosis of an edentulous mandible 2 years after a calculated 6000 cGy dose in 6 weeks given with telecobalt therapy. Entire angle of the jaw has separated. B, Soft tissue and mandibular necroses have healed. Function is good. Patient refused any attempt at closure of fistula.
Nasopharyngeal Carcinoma

- Generally treated with irradiation
- Prognostic factors
- Neoadjuvant chemotherapy important
- Treatment portals
- Customize radiation beams and energy doses to spare spinal cord and mandible
- Complications include cranial nerve palsies, radiation myelitis, and hypopituitarism and trismus
Hypopharynx

- T1 and T2 can be treated with irradiation or conservation surgery
- Vocal cord fixation is a contraindication to irradiation
- Postop irradiation increases local regional control for larger lesions
- Treatment portals
- Complications include pc fistula
Larynx

- T1 and T2 carcinoma can be treated with xrt or surgery
- Advanced cancers treated with combined modality
- Indications for postop irradiation
- Treatment portals
- Lymphatics included for early supraglottic tumors - control is poorer for supraglottic lesions
- Side effects can involve voice, laryngeal edema, mucositis and dysphagia
Brachytherapy

- Radioactive sources placed close to the target
- Temporary and permanent implants
- Advantages
  - Entire tumor must be accessible
  - Lymph node metastases preclude sole use of brachytherapy
Case Presentation
60 yo WM with sore throat

- History includes 3 months of sore throat, odynophagia, weight loss, neck lump and no other symptoms
- PMH significant for diabetes, poorly controlled hypertension on several meds
- Social History significant for 50 pack year smoking and moderate etoh use
Case continued

- PE reveals man appearing older than stated age
- H&N exam reveals 3 cm exophytic right tonsillar lesion with right level II lymph node of 3 cm
- Rest of H&N exam is wnl
- Rest of PE is wnl
Case continued

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