Objectives (topics to cover)

- A few fundamentals of radiobiology (clinical considerations)
- Treatment planning
- Quick overview of staging/work-up and treatment of
  - Lung cancer
  - Breast cancer
  - Prostate cancer
  - H&N cancer

How Does Radiation Therapy Work?

- Biologic effects of radiation are from DNA damage
- Direct DNA damage is when an electron interacts with DNA
- Indirect DNA damage is when an electron interacts with water to produce a hydroxyl radical which in turn damages the DNA

Acute/Late Effects of RT

- Dependent upon
  - Volume treated
  - Total dose delivered
  - Dose per fraction
  - Time span over which treatment delivered
  - Other prior or concurrent therapies
  - Tissue types within field
4 Rs of Radiobiology
(Explains the Benefits of Fractionation)

- Repopulation: normal tissue
- Repair: normal tissue
- Redistribution: tumor
- Reoxygenation: tumor

Repair (of sublethal damage)

- simply the repair of double-strand DNA breaks
- refers to the increase in cell survival when a dose of radiation is split into 2 fractions separated by time
- Dose-Rate Effect
  - When the radiation dose rate is reduced, a reduction in cell killing occurs because sublethal damage repair occurs during the protracted exposure

Re-oxygenation

- Oxygen effect:
  - Cells are much more sensitive to killing by radiation in the presence of oxygen

Repopulation (tumor)

- Surviving cancer cells go into overdrive and divide faster and faster
- Protracting radiation for too long can result in reduced cancer cure
- We use altered fractionation to overcome this problem

Re-oxygenation

- Tumors have both aerated and hypoxic cells
- A given dose of x-rays kills a greater proportion of aerated cells than hypoxic cells
- surviving cells (presumably the hypoxic cells) re-oxygenate themselves after a period of time

Altered Fractionation

- Hyperfractionation:
  - use of smaller doses per treatment (1.1-1.2 Gy)
  - allows higher total doses in a given time, without increasing late side effects
  - Radiosensitization through cell cycle redistribution
  - Increases acute effects
Altered Fractionation

• Accelerated fractionation:
  – Reduction in overall treatment time reduces chance for tumor repopulation
  – Increase probability of tumor control
• Different ways to accelerate radiation
  – Twice daily
  – Concomitant boost
  – Increasing total dose per week (6 fxns/week)

Dose Escalation

• Increase total dose (standard fractionation)
• Hypofractionation
  – “Biologically effective dose”
  – Increases EFFECTIVE dose by increasing dose/fxn
  – SRS/SBRT

TREATMENT PLANNING

Definitions

• GTV-gross tumor volume
• CTV-clinical tumor volume
• ITV-internal tumor volume
• PTV-planning target volume
• Block margin

Target Delineation

• GTV: visible tumor as seen on CT or other imaging studies
• CTV: visualized tumor plus regions at risk such as microscopic extension of disease and nodal chains
• PTV: expanded CTV to include setup errors, patient motion, linear accelerator alignment errors, and other uncertainties
• Delineation of GTV, CTV, and PTV are even more important for IMRT as the delineated contours are used as direct input to computer optimization algorithm as it attempts to produce dose distributions that conform to target while sparing normal tissues
STAGING

• Staging may be
  – clinical (physical exam, biopsy, endoscopy, imaging studies)
  – pathologic (surgical resection/microscopic exam)

H&N Cancer

Oropharynx

• Subsites: soft palate, palatine tonsils, tonsillar pillars, BOT (lingual tonsils), pharyngeal wall
• Anatomic boundaries
  – Sup: plane of superior surface of soft palate
  – Inf: superior surface of hyoid (floor of vallecula)

Staging of Oropharyngeal Cancer

• T1: ≤2cm in greatest dimension
• T2: >2cm but ≤4cm
• T3: >4cm
• T4a: Invades larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate or mandible
• T4b: Invades lateral pterygoid, pterygoid plates, lateral nasopharynx, skull base, encases internal carotid artery

• N1: Single ipsi LN ≤3cm
• N2a: Single ipsi LN >3cm but ≤6cm
• N2b: Multi ipsi LNs ≤6cm
• N2c: Bilateral or contralateral LNs all ≤6cm
• N3: LN >6cm

• III: T3N0, T1-3N1
• IVA: T4aN0-1, T1-4aN2
• IVB: T4b, N3
• IVC: M1
**Work Up**

- History & physical examination
- Biopsy
- Flexible fiberoptic laryngoscopy
- CT neck/chest (or PET/CT)
- Dental evaluation
- IR for feeding tube

**Current Standard of Care Treatment**

- IMRT to primary site and bilateral neck
  - PTV1: 6930 cGy/210 cGy
  - PTV2: 5940 cGy/180 cGy
  - PTV3: 5610 cGy/170 cGy (or 5400 cGy)
- Concurrent sensitizing systemic therapy
- +/- induction chemotherapy (cases of bulky primary or N3 disease)

**Planning RT**

- IMRT used to improve sparing of adjacent critical structures
- Planning:
  - GTV1: Primary tumor and involved LNs
  - CTV1: GTV1 + ~1 cm
  - CTV2: High-risk subclinical disease, first echelon LNs
  - CTV3: Low-risk subclinical disease (contralateral neck)
  - OAR: Salivary structures, oral cavity, left/right inner ear, larynx, esophagus-inlet (including constrictor muscles), mandible, spinal cord
  - PTVx = CTVx + set-up margin

**Planning Priorities and Coverage**

**Priorities**

1. Cover PTV with prescription
2. Spare critical normal structures
3. Parotid sparing (particularly contralateral if need to sacrifice ipsilateral)

**Coverage**

- ≥93% isodose line should cover 100% PTV1
- ≤20% of any planning target volume to receive >110% of the prescribed dose
- Hot spots 110-117% typical with IMRT

**LNss At Risk**

- Level IB (submandibular nodes): Ipsilateral in all cases except primary palate tumors which do not extend to the tonsil or base of tongue
- Parapharyngeal nodes: Ipsilateral in all cases
- Levels II-IV: all cases, bilaterally
- Level V (posterior cervical): all cases when level II-IV are involved
- Retropharyngeal nodes: ipsilateral all cases – both if tumor crosses midline
Summary – Dose Constraints

Key points:
- Verrucous carcinoma can be reduced by limiting the mean dose to 20 Gy for one-parotid gland, ≤ 15 Gy to the noninvolved submandibular gland and ≤ 50 Gy to the neck cavity.
- Larynx sparing can be reduced by keeping the mean dose ≤ 50 Gy to the noninvolved paraglottic constrictor muscles and the larynx.
- Hearing loss might be reduced by limiting the dose to the inner ear to ≤ 45-54 Gy.
- Laryngeal and temporal lobe radiation necrosis could result if the temporal lobes are treated with a maximum dose of ≤ 50 Gy, or if 1% of the temporal lobe volume receives ≥ 50 Gy.
- By limiting the maximum dose to the optic nerve and brain to 54 Gy, the risk of lobe radiation-induced optic neuropathy can be minimized.
- Reductions in dose to the salivary glands and mandible are likely to translate into reduced incidence of xerostomia and stomatitis.


Table 3: Overview of studies assessing critical structures for larynx sparing

Larynx/Pharyngeal Constrictor Sparing IMRT

PEG Dependence vs. Use of L/E Constraint

Parotid-Sparing IMRT

Use of the L/E OAR

In daily IMRT planning, the larynx and esophageal-inlet can be delineated as a single organ at risk, with a planning objective of mean dose ≤ 50 Gy. This single constraint limits the dose to the larynx, esophagus and PC muscles, expediting recovery from swallowing dysfunction.
**BREAST CANCER**

**Important for Diagnosis**
- Clinical exam
- Bilateral diagnostic mammogram
- U/S of breast + axilla
- U/S-guided or stereotactic biopsy of suspicious breast lesions or calcifications
- Biopsy of axilla for clinically positive LNs
- MRI of the bilateral breasts (as indicated)

**STAGING**

**Clinical Nodal Staging**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor ≤ 30 mm in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤ 1 mm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt; 1 mm but ≤ 5 mm in greatest dimension</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor &gt; 5 mm but ≤ 10 mm in greatest dimension</td>
</tr>
<tr>
<td>T1d</td>
<td>Tumor &gt; 10 mm but ≤ 20 mm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 20 mm but ≤ 50 mm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 50 mm in greatest dimension</td>
</tr>
</tbody>
</table>

T4a: Tumor of any size with direct extension to the chest wall and/or to the skin (infiltration or skin nodules)

T4b: Extension to the chest wall, not including only pectoralis major muscle involvement

T4c: Infiltration of skin or subcutaneous fat, and/or skin ulceration and/or palpable satellite nodules, and/or evidence of bone (or bone shadow) at the site, which do not meet the criteria for inflammatory carcinoma

T4d: Inflammatory carcinoma (see “Rules for Classification”)

T0: No regional lymph node metastases

N0: No regional lymph node metastases

N1: Metastasis to axillary lymph node(s)

N1a: Metastasis to axillary lymph node(s) not fixed or immovable

N1b: Metastasis to axillary lymph node(s) fixed or immovable

N2: Metastasis to pectoral, interpectoral, or infrapectoral lymph node(s) or other lymph node(s) not fixed or not immovable

N2a: Metastasis to pectoral, interpectoral, or infrapectoral lymph node(s) fixed or immovable

N2b: Metastasis only clinically detected in pectoral, interpectoral, or infrapectoral lymph node(s) or other lymph node(s) not fixed or not immovable

N3: Metastasis to internal mammary lymph node(s) or other lymph node(s) fixed or immovable

N3a: Metastasis to internal mammary lymph node(s) fixed or immovable

N3b: Metastasis to internal mammary lymph node(s) not fixed or not immovable

N3c: Metastasis to internal mammary lymph node(s) not fixed or not immovable

N4: Metastasis to contralateral breast(s) or other organ(s)
Female Breast Cancer Survival by Stage
Work-up

NCCN Treatment Guidelines

Radiation Treatment as Part of a Breast Conservation Approach

7 RCTs Showing LC Benefit for RT following Lumpectomy

Summary of RT Benefit

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- 2/3 risk reduction in ipsilateral breast cancer recurrence with XRT
- 20-30% reduction in local recurrence risk
- 5% benefit in overall survival from metaanalysis
- 4:1 Ratio frequently cited meaning prevent 4 local recurrences, avoid 1 breast cancer related death

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EBCTCG meta-analysis of 10,801 women in 17 RCTs, the addition of RT to Lumpectomy reduced LR by ~50%
**1 breast cancer death avoided by 15 yrs for every 4 recurrences prevented by 10 yrs**
Can we shorten the treatment course?

- T1-2N0
- Majority T1 and >50 y.o
- No Boost

12-Y Results:
- Same LC
- Same OS
- Same cosmesis

Whelan, SABCS 2007
Hypofractionated RT for Breast Cancer

- "Conventionally fractionated" RT schedules deliver therapy over 5–6 weeks, often followed by 1–2 weeks of boost therapy
- Recent studies have demonstrated equivalent tumor control and cosmetic outcome in specific patient populations with shorter courses
- "Choosing Wisely" - “Don’t initiate whole breast radiotherapy as a part of breast conservation therapy in women age ≥50 with early stage invasive breast cancer without considering shorter treatment schedules”

ACCELERATED PARTIAL BREAST IRRADIATION

What about partial breast irradiation?

- APBI = Accelerated Partial Breast Irradiation
  - Whose eligible?
    - T1, N0, > 60, unicentric, ER+
  - Accelerated = Treatment length 6 weeks ➔ 1 week
  - Treatment is twice a day
  - Partial Breast = Coverage of tumor bed plus a margin

Breast Brachytherapy = Internal radiation

- Balloon placed in lumpectomy cavity
- Central catheter is hollow so radioactive source on wire can travel into center of balloon
- APBI: 34 Gray in 10 fractions BID
- 3.4 Gray per dose, 6.8 Gray per day

APBI – Axial View

LUNG CANCER
NSCLC Work-Up

- H & P
- Labs
- Imaging:
  - CT chest/abdomen, PET/CT
  - MRI Brain
- Pathologic confirmation of disease
  - Thoracentesis for pleural effusions
  - Bronch for central lesions, CT-guided bx for peripheral
- Mediastinoscopy or bronch bx to confirm CT or PET + nodes
- Pulmonary function testing

Staging: T-Stage

- T1- 3cm or less, completely surrounded by lung or visceral pleura, no involvement more proximal than the lobar bronchi
- T2- Greater than 3cm, involvement of visceral pleura, involvement of main stem bronchi >2cm from carina, atelectasis or obstructive pneumonitis involving less than the entire lung
- T3- Involvement of chest wall, diaphragm, mediastinal pleura or parietal pericardium, involvement of mainstem bronchi <2cm from carina, atelectasis or obstructive pneumonitis involving entire lung
- T4- Involvement of carina, trachea, esophagus, mediastinum, heart, great arteries; separate tumor nodule in same lobe or malignant pleural effusion

N- Stage

- N1- Ipsilateral peribronchial or hilar lymph nodes (Nodal stations 10-14)
- N2- Ipsilateral mediastinal or subcarinal lymph nodes (Nodal stations 1-9)
- N3- Contralateral mediastinal or hilar lymph nodes, Ipsilateral or contralateral scalene or supraclavicular lymph nodes

Stage Grouping

- IA  T1N0M0
- IB  T2N0M0
- II A  T1N1M0
- II B  T2N1M0  T3N0M0
- III A  T3N1M0  T1-3N2M0
- III B  T4NxM0  TxN3M0
- IV  TxNxM1
Evolution of Treatment Planning & Delivery for Lung Cancer

2D Radiation technique

IMRT
Intensity-Modulated Radiation Therapy
Inverse Planning
Summary of Management of Stage III Lung Cancer

- **IIIA**
  - Neoadjuvant chemoRT → surgical resection
  - Definitive chemoRT
- **IIIB**
  - Definitive chemoRT

Prostate Cancer: Epidemiology

- #1 non-cutaneous cancer in men and 2nd leading cause of death (behind lung cancer)
- 1/6 men diagnosed in their lifetime and 1/36 die of disease
- Median age at diagnosis is 70
- ~85% multifocal disease
- Almost always (>95%) adenocarcinomas, also see small cell carcinomas
Understanding Gleason Score

TNM Staging

- Sources and Studies vary slightly on exact definitions
- Basic Principle
  - Takes into account: Gleason score, PSA, T stage
  - Highest grade of any single of risk factor up-stages your risk
    - T Stage
      - T1a-c = Low Risk
      - T2 = Intermediate Risk
      - T3 = High Risk
    - Gleason
      - ≤6 = Low Risk
      - 7 = Intermediate Risk
      - ≥8 = High Risk
    - PSA
      - ≤10 = Low Risk
      - 10-20 = Intermediate Risk
      - ≥20 = High Risk

Risk Stratification

Low Risk: NCCN Treatment Recommendations

- Active surveillance
  - PSA at least as often as every 6 mo
  - DRE at least as often as every 12 mo
- Active surveillance
  - PSA at least as often as every 6 mo
  - DRE at least as often as every 12 mo
  - Repeat prostate biopsy as often as every 12 mo

External Beam Radiation Therapy

- Uses high energy photons to treat a targeted area of the body
- Does not hurt, cause hair loss or nausea
- Does not make you radioactive
- Treatment done using low dose beams from various angles
- Images will be taken daily to ensure treatment set up accurate
- Each treatment takes 15-20 minutes
- Given over 5.5 to 9 weeks of daily treatments
Brachytherapy

- Uses a trans-rectal ultrasound to visualize the prostate
- Needles are inserted into the prostate gland through the perineum
- Tiny radioactive seeds are then permanently implanted
- Dose given off over approximately 6 months
- Procedure takes about 2 hours
- Discharged home the same day

Kupelian. 2004 IRJOB
Pooled Analysis of Cleveland Clinic and Memorial Sloan Kettering
2,991 consecutive Patients
RP vs EBRT <72 Gy vs EBRT >72 Gy vs Seeds vs Combo (EBRT+seeds)
Patients in RP group younger with more favorable characteristics

5 year biochemical PFS
- RP: 81%
- <72 Gy: 51%
- >72 Gy: 81%
- Seeds: 83%
- Combo 77%

Conclusion: Treatments equivalent as long as >72 Gy used for EBRT

In general . . .

- In clinic, when we discuss outcomes for Low Risk Prostate for
  - Radical Prostatectomy
  - External Beam Radiation
  - Permanent Seed Implants

- We counsel patients that these approaches are basically thought to have equivalent outcomes but often quite difference side effect profiles . . .

2.5 Gy/fraction x 28 fxns = 1.8 Gy/fraction x 42-44 fxns
Intermediate Risk: NCCN Treatment Recommendations

- Active surveillance:
  - PSA as often as every 3 mo
  - DRE as often as every 12 mo
- <10 y
- >10 y
- Radical prostatectomy with pelvic lymph node dissection if predicted probability of lymph node metastasis >2%
- RT (3D-CRT/IMRT with daily IGRT) + short-term neoadjuvant/adjunctive ADT (4-6 mo) + brachytherapy

High Risk: NCCN Treatment Recommendations

- Clinically Localized:
  - High-risk:
    - RT (3D-CRT/IMRT with daily IGRT) + long-term neoadjuvant/adjunctive ADT (2-3 y) (category 1)
    - or
    - RT (3D-CRT/IMRT with daily IGRT) + brachytherapy + short-term neoadjuvant/adjunctive ADT (4-6 mo)
    - or
    - Radical prostatectomy + pelvic lymph node dissection (selected patients with no fixation)

* Radiation therapy may be needed post-operatively for high risk disease if there are positive surgical margins or evidence of extra-prostatic extension

Questions?

Radiation Therapy for High-Risk Prostate Cancer