RADIATION THERAPY: PEARLS FOR THE GENERALIST

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• Disclosures – None
• Off-label usage – None
Radiation, a big black box.....
What to Expect

• Questions my patients ask
• Crash course in radiation oncology
• 3 cases
  • Case with audience question
  • Brief literature review
  • Conclusions and recommendations
  • Clinical pearl
Common Questions my patients ask

• Is there a big red button?
• Does radiation make a zzzzzzzzt noise?
• Will I be radioactive?
• Will I get superpowers?
• Can I read at night by the glow of my body?
Common Questions my patients ask

• What is radiation?
• Why does it usually take several weeks?
• Does it work right away?
• Can it be curative?
Radiation Oncology - Crash Course

• Radiation Oncology
  • Electromagnetic radiation to treat cancer
  • DNA damage by ionizations and free radicals
• Tumor and normal cells have differential ability to repair DNA
• Giving total dose in small daily fractions
  • Allows normal cells to repair
• Effects from cumulative dose
• Can be curative
Radiation Oncology – Crash course

• Early effects – acute inflammation/damage
  • Mucositis
  • Pneumonitis, pericarditis
  • Tumor response

• Late effects – fibrosis and vascular changes
  • Coronary disease
  • Organ dysfunction
  • Second malignancies
The Problem

• As we make progress in cancer treatment, more people are long term survivors

• Patients commonly transition long term follow-up to their primary care provider

• The following cases are scenarios I encountered in my internal medicine practice
Case 1
Case 1
68M base of tongue cancer

- Locally advanced base of tongue squamous cell carcinoma with bilateral neck lymph nodes
- Treated 6 years ago with a 7 week course of RT and chemotherapy
- Cancer free at last oncologic checkup 1y ago
- Presents to primary physician with a 3m history of fatigue
Case 1
68M base of tongue cancer

Given his oncologic history, what is the most likely etiology for his fatigue?

1. Recurrence of his primary tumor
2. Radiation-induced secondary malignancy
3. Anemia from his cancer treatment
4. Hypothyroidism
5. Hypopituitarism
Case 1
68M base of tongue cancer

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Case 1
68M base of tongue cancer

1. Recurrence of his primary tumor
   • Squamous carcinomas of the head and neck rarely recur after 5y

2. Radiation-induced secondary malignancy
   • RT induced cancers are very rare and usually >10-15y after RT as adults

3. Anemia from his cancer treatment
   • Acute effect

4. Hypothyroidism

5. Hypopituitarism
   • Rare for head and neck RT to give meaningful pituitary dose
Case 1
68M base of tongue cancer
Treatment fields
Case 1
Late radiation effects on the thyroid

- Hypothyroidism in head and neck pt after RT
  - 48% at 5y
  - Up to 67% at 8y
- Median time to hypothyroidism is 1.5 years
- Studies find both clinical and subclinical hypothyroidism
  - Subclinical 23-53%
  - Clinical 11-33%

Boomsma, et al, IJROBP 2011
Mercado, et al, Cancer 2011
Case 1
Late radiation effects on the thyroid

• Recommendation for follow-up
  • Yearly TSH and thyroid exam in patients who received radiation to the neck
    • Most head and neck patients
    • Many Hodgkin lymphoma patients
    • Some Upper spine RT
    • Some upper lung RT
Case 1
Clinical Pearl

• Hypothyroidism is common after radiation therapy to the neck, and screening should be routinely performed.
Case 2
Case 2
25F survivor of Hodgkin Lymphoma

- 25 year old woman presents for a GME
  - She had Hodgkin Lymphoma of the mediastinum treated with chemotherapy and radiation at age 20
  - No symptoms or complaints
Case 3
25F 5 year survivor of Hodgkin Lymphoma

When should breast cancer screening start in this patient who received chest radiation at the age of 20?

1. Age 21
2. Age 25
3. Age 28
4. Age 30
5. Age 40
Case 3
25F 5 year survivor of Hodgkin Lymphoma

When should breast cancer screening start in this patient who received chest radiation at the age of 20?

1. Age 21
2. Age 25
3. Age 28
4. Age 30
5. Age 40
Case 2
Breast Cancer Risk – Hodgkin Lymphoma

- Up to 30-fold increased breast cancer risk over general population
- Median onset 18-20 years after RT, risk starts 5-9 years after RT
- 30 year risk of secondary breast cancer in Hodgkin Lymphoma patients receiving RT
  - 19% incidence all patients
  - 26% if RT before age 21
  - <10% (not increased over general population) if after age 40

Hodgson et al, JCO 2007
De Bruin et al, JCO 2008
Case 2
Breast Cancer Risk – Hodgkin Lymphoma

Fig 2. The cumulative incidence of breast cancer (BC) after Hodgkin’s lymphoma. (A) Cumulative risk and incidence of BC (invasive BC [IBC] + ductal carcinoma in situ [DCIS]). (B) Cumulative incidence of BC (IBC + DCIS) according to age at first treatment. (C) Cumulative incidence of IBC according to radiation fields and population-expected risk.

De Bruin et al, JCO 2008
Case 2
Breast Cancer Risk – Hodgkin Lymphoma

• Reduction of RT volumes decreases risk, but still present
  • Mantle field 2.7 fold risk over limited field

Hodgson et al, JCO 2007
De Bruin et al, JCO 2008
Case 2
Mantle Field – Hodgkin Lymphoma
Case 2
Involved nodal RT – Hodgkin Lymphoma
Case 2
Breast Cancer Screening - Recommendation

• Breast cancer screening in patients who received chest RT:
  • Monthly self breast exam
  • Yearly clinical breast exam until age 25, then every 6 mo
  • Yearly mammogram and breast MRI starting at age 25 or 8 years after treatment, whichever comes LAST

www.survivorshipguidelines.org
Warner et al, NEJM 2004
Sung et al, Radiology 2011
Case 2
Clinical Pearl

• Patients with chest radiation prior to the age of 40 years are at increased risk for breast cancer, and screening should start earlier and include MRI.
Back to Case 2
Case 2
25F survivor of Hodgkin Lymphoma

• She also heard she has a higher risk for cardiovascular disease and asks about screening and prevention.
Case 2
25F survivor of Hodgkin Lymphoma

• Cardiac mortality 2x to 7x higher in survivors of childhood Hodgkin lymphoma than controls

• Latency for symptomatic disease 5-20y after RT
  • RR of Acute MI 3.1 at 22y
  • Highest risk if RT before age 20 (RR 44)
  • Lowest risk if RT after age 49 (RR 1.8)

Hancock et al, JAMA 1993
Heidenreich et al, J Am Coll Cardiol 2003
Case 2
Late RT effects on the heart – At 20 years

- Coronary artery disease (ostia)
  - 10% symptomatic

- Valvular disease (Aortic and Mitral)
  - 5% Clinically important
  - 16-50% by imaging

- Cardiomyopathy
  - CHF 7.9%
  - RWMA 29% (3-6x risk)
  - Diastolic dysfunction 23% (7x risk)

Hull et al, JAMA, 2003
Heidenreich et al, J Am Coll Cardiol , 2003
DeBruin et al, Blood 2007
Case 2
Late RT effects on the heart

- Morphologic changes in RT-induced CAD similar to spontaneous CAD
- RT may initiate/promote atherosclerosis, but RT-associated CAD rare without other CV risk factors

Carver et al, JCO, 2007
Case 2
Late RT effects on the heart

Table 5. Factors Increasing the Risk of Cardiac Sequelae After Mediastinal Radiation Therapy

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Radiation factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated anthracyline chemotherapy</td>
<td>Orthovoltage radiation (rarely used since the 1970s)</td>
</tr>
<tr>
<td>Location of tumor close to heart border*</td>
<td>Volume of irradiated heart*</td>
</tr>
<tr>
<td>Age &lt; 18 years</td>
<td>Total dose to the heart &gt; 30 Gy</td>
</tr>
<tr>
<td>Associated cardiac risk factors</td>
<td>Daily dose fraction &gt; 2 Gy/day</td>
</tr>
<tr>
<td>Baseline cardiac disease*</td>
<td>Absence of subcarinal blocking</td>
</tr>
<tr>
<td>&gt; 10 year post-radiation therapy</td>
<td></td>
</tr>
</tbody>
</table>

*These factors are consensus based and not individually validated.

Carver et al, JCO, 2007
Case 2
Late RT effects on the heart

• Modern techniques decrease risk of cardiac sequelae
  • Decreased dose
  • Decreased field size
  • Improved targeting
  • Improved RT delivery and dose distribution
    • Pericardial disease: 20% → 2.5%
    • Abnormal EF: 57% → 4%
    • CV death in breast cancer: 15% → 5.5%

Carver et al, JCO, 2007
Giordano et al, JNCI, 2005
Case 2
Late effects on the heart – Recommendation

• For long term (>5y) survivors cancer who have received mediastinal RT before age 50
  • The treating oncologist should be involved in determining frequency and type of cardiac screening
  • RT to the mediastinum should be considered a risk factor for heart disease
• Excellent website: www.survivorshipguidelines.org
Case 2
Clinical Pearl #2

• Survivors of childhood Hodgkin lymphoma have an increased risk of cardiovascular disease, but RT induced coronary disease is rare in absence of traditional risk factors. Chest radiation should be considered an additional risk factor.
Case 3
2 men with prostate cancer

• 2 65y identical twin brothers are simultaneously diagnosed with early stage, favorable risk prostate cancer.

• Gleason 3+3, PSA 4.8, small palpable nodule.

• They each choose a different modality of treatment
  • Pt 1: radical prostatectomy
  • Pt 2: external beam radiation
Case 3
2 men with prostate cancer
Pt 1: Radical prostatectomy

PSA 3mo after surgery is <0.1 ng/ml. He asks how he would know if the cancer comes back. What is the definition of biochemical relapse in this pt?

1. Any detectable PSA value
2. PSA $\geq 0.2$, with a repeat value $>0.2$
3. PSA $\geq 1$ with a repeat value of $>1$
4. Any PSA value $>2$
5. When the PSA increases to the pre-treatment PSA value (4.8 in this patient)
Case 3
2 men with prostate cancer
Pt 1: Radical prostatectomy

PSA 3mo after surgery is <0.1 ng/ml. He asks how he would know if the cancer comes back. What is the definition of biochemical relapse in this pt?

1. Any detectable PSA value
2. PSA ≥0.2, with a repeat value >0.2
3. PSA ≥1 with a repeat value of >1
4. Any PSA value >2
5. When the PSA increases to the pre-treatment PSA value (4.8 in this patient)
Case 3
Pt 1: Radical prostatectomy – PSA recurrence

• PSA after prostatectomy should be undetectable
• PSA relapse 15% at 15y after prostatectomy for low risk disease
• 50% with PSA 0.2 have progressive increase
  • 34% develop mets, at a median of 8 years
• 75% with PSA 0.4 will have progressive increase
• Salvage radiation effective in >50-65%

Pound et al, JAMA 1999
Beresford et al., Clin Oncol 2010
Case 3
2 men with prostate cancer
Pt 2: External beam radiation

• Pt 2 undergoes external beam radiation. His PSA was slowly decreasing after radiation treatment, but increased at his 24mo visit.
  • preRT 4.8
  • 3mo 0.69
  • 6mo 0.3
  • 9mo 0.25
  • 12 mo 0.14
  • 18 mo 0.19
  • 24 mo 0.45
Case 3
2 men with prostate cancer
Pt 2: External beam radiation

PSA decreased after RT to a nadir of 0.14, but increased at 24mo to 0.45.

What level of PSA signifies a recurrence in this patient treated with radiation for prostate cancer?

1. Any detectable level (no tx response)
2. ≥0.2, with a repeat value >0.2
3. Any value >1
4. Nadir plus 2
5. 3 consecutive rises after nadir
Case 3
2 men with prostate cancer
Pt 2: External beam radiation

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Case 3
Pt 2: External beam radiation – PSA Response

• RT different than after surgery
  • Normal prostate cells remain, can produce PSA
  • Normal prostate cells can increase PSA production with age
  • Radiation effect can take months to years
  • PSA declines approximately by 80% at 3 months, then slowly decreases to nadir
    • Median 2 years to nadir

Abramowitz, et al, Cancer 2008
Roach et al, IJROBP 2006
Case 3
Pt 2: External beam radiation

• PSA Recurrence
  • Definition of biochemical recurrence after RT (external or brachytherapy seeds) is nadir +2 ng/ml

Abramowitz, et al, Cancer 2008
Roach et al, IJROBP 2006
Horowitz et al, Cancer, 2006
Case 3
Pt 2: External beam radiation

• Pt 2 wonders why his PSA has increased 2 years after RT even if it doesn’t qualify as a PSA failure.

• This likely represents a “PSA bounce”

Abramowitz, et al, Cancer 2008
Roach et al, IJROBP 2006
Case 3
Pt 2: External beam radiation

• “PSA bounce”
  • Minimal rise of 0.4 ng/ml over 6m, followed by drop of any magnitude

• Occurs in 20-30% pt treated with RT
  • Median time 18m after RT
  • Median magnitude 0.4 ng/ml
  • Duration 14m
  • May predict for future failure (58% vs 72% PSA control at 10 years)

Abramowitz, et al, Cancer 2008
Roach et al, IJROBP 2006
Horowitz et al, Cancer, 2006
Case 3
2 men with prostate cancer
Recommendations for following PSA

• Followup PSA and DRE
  • Every 3m first year
  • Every 6-12 m next 4 years, then yearly
• Postsurgical pt should have undetectable PSA
  • ≥ 0.2, with repeat >0.2 suggests recurrence
• Post RT patients should have decreasing PSA to nadir, which can take ≥ 2 years
  • PSA bounce can occur 18m to 3 y after RT
  • 2 ng/ml over nadir is considered recurrence

Abramowitz, et al, Cancer 2008
Roach et al, IJROBP 2006
Horowitz et al, Cancer, 2006
Case 3
Clinical Pearl

• PSA after surgery for prostate cancer should be undetectable and a biochemical recurrence is defined as a PSA $\geq 0.2$. PSA after radiation therapy for prostate cancer should decrease to a nadir over several months and a biochemical recurrence is defined as the nadir PSA plus 2.
Thank you!
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