ARROCase: Management of Chest Wall Toxicity After SBRT

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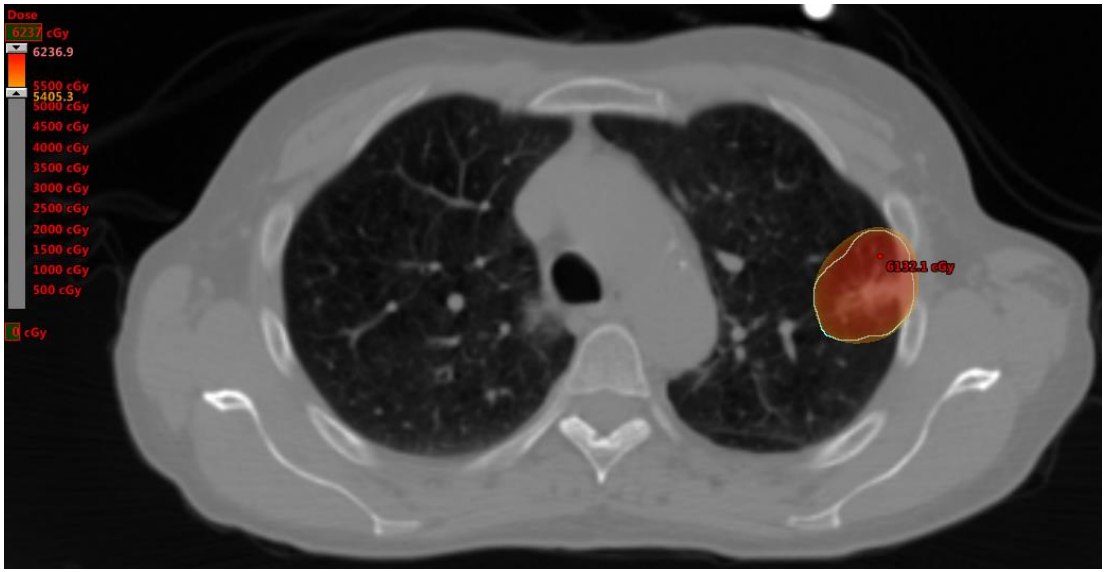
Case Presentation

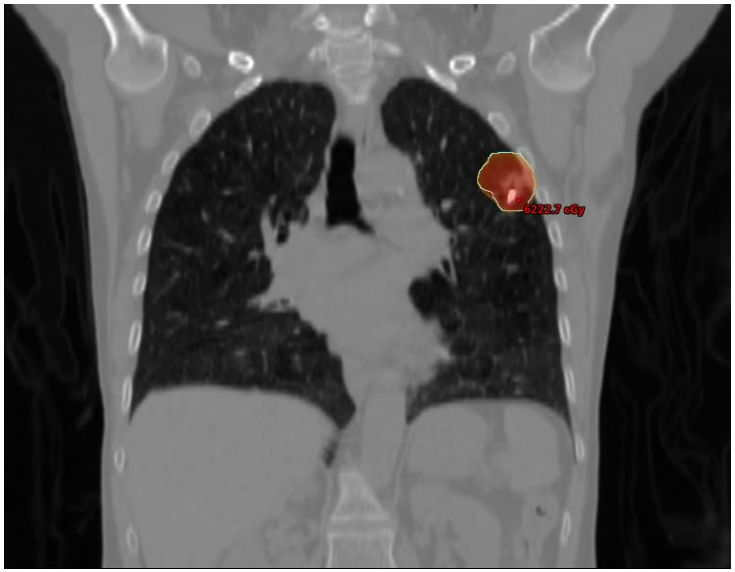
- 57 y/o woman w/ presumed Stage I NSCLC of LUL s/p SBRT to 60 Gy, anxiety, and COPD.
- Follow up 15 months post-SBRT c/o left axillary pain that wrapped around to her breast; also experienced three months prior, at which time it subsided spontaneously
- She started working a more labor-intensive job that required lifting heavy boxes

Case Presentation (cont)

- Pain
  - Exacerbated with movement, rolling over in bed, or lifting items at work, sometimes causing her to take time off
  - Refractory to lidocaine cream, ibuprofen, hydrocodone-acetaminophen
- CT chest without significant abnormality

Radiation Plan





<u>Plan Parameters for Chest Wall</u>

V_{30}: 17 cc

$D_{2\ cc}$: 56.1 Gy

$D_{30\ cc}$: 24.4 Gy

$D_{70\ cc}$: 17.5 Gy

Max dose: 60.4 Gy

Questions

- What ways can we assess pre-procedure risk of chest wall toxicity (CWT) secondary to SBRT?
- What management options exist to manage CWT?

SBRT Complications for Peripheral Tumors

- Acute: fatigue, skin toxicity, CWT, nausea
- Late: radiation pneumonitis, CWT, rib fracture

Predictive Factors for CWT

- No single variable has been consistently identified across studies
  - No consistent definition of the chest wall organ at risk (OAR)
  - In some studies no chest wall OAR is defined
  - Endpoints differ (e.g. severity)
  - Toxicity (e.g. fracture) and symptoms do not always correlate

Dose-Response Modeling

- Dunlap *et al*. *IJROBP* 2010; 76(3): 796-801.
  - One of the earliest studies explicitly devoted to studying the risk of CWT in relation to dose exposure
  - Retrospective study of 60 consecutive patients receiving SBRT to the lung in three to five fractions and a max chest wall (CW) dose of ≥20 Gy
  - Median onset of severe CW pain and/or rib fracture was 7 months
  - CW exposure of 30 Gy best predicted risk of CW pain and/or rib fracture
    - No toxicity observed with a treated CW volume < 30 cc

Dose-Response Modeling (cont)

- Kimsey *et al*. *Semin Radiat Oncol.* 2016 26:129-34.
- Pooled analysis of 170 patients who underwent lung SBRT using a LINAC (126; based on analysis by Mutter *et al*. 2012) or CyberKnife (44)
- Constructed an updated dose-response model for grade >1 CWT

Methods

- Based on DVH atlas of 2- and 3-cm thick CW contours over 3, 4, and 5 fractions by Mutter 2012
  - Two-cm contours found to best correlate with CW pain
  - Fifteen-month time point used for the analysis
- Assumed $\alpha/\beta = 3$
- Four-fraction dose equivalents (median duration in combined data set) were calculated prior to conducting the analysis
- Statistical dose-tolerance limits for $D_{70\ cc}$, $D_{30\ cc}$, $D_{2\ cc}$, and D_{max} were obtained from the model

Results

- At 15 months:
  - LINAC group had 27/126 (21%) patients experienced grade >1 toxicity
  - CyberKnife group had 2/44 (5%) patients with grade 2 toxicity, 0 with grade >2 toxicity
  - Dose-response was significant for $D_{30\ cc}$ and $D_{70\ cc}$, with slope < 1 (i.e. <1% increase in risk of toxicity with 1% increase in dose)

Summary 1

- Predicting risk of CWT based on available data/studies is difficult due to inconsistency of data collection and parameter definitions
- Pre-treatment risk assessment is ever evolving
  - CW V_{30} is a well studied parameter to guide risk of CWT
  - $D_{30\ cc}$ and $D_{70\ cc}$ found to be significant dose-response predictors in the Kimsey study
  - Higher risk of (grade 2) toxicity may be reasonable to accept in select cases
- Limited radiation-based management options
  - Drop the total dose
  - Alter fractionation
  - PTV coverage should not be compromised while attempting to limit dose to the CW (though minimizing dose to this OAR is important)

Non-pharmacologic Agents

- Examples: hot/cold packs
- Pros:
  - Cheap
  - Easy to apply
  - Widely available
- Cons:
  - Short duration of action
  - Cumbersome if patient is active
  - Severity of pain likely to exceed what these are able to palliate completely

NSAIDs

- Examples: ibuprofen, naproxen, ketorolac
- Pros:
  - Anti-inflammatory mechanism of action
- Cons:
  - The common stuff: ulcerations/GIB, renal dysfunction
  - May not be targeting the appropriate pain mechanism or all mechanisms responsible for a patient's discomfort

Topical Agents

- Examples: patches/creams (lidocaine)
- Pros:
  - Creams are relatively inexpensive
  - Minimal side effects
- Cons:
  - Short duration of action
  - Localized treatment, shallow penetration
  - Difficult to apply depending on location, social supports
  - Patch formulations can be expensive
  - Body habitus may impact absorption/bioavailability

Corticosteroids

- Example: dexamethasone
- Pros:
  - Short courses of therapy tolerated well
- Cons:
  - Not the best option for chronic use (side effects, mechanism of pain)
  - Careful use in diabetics given (very small) risk of grade 3 or 4 hyperglycemia

Opioids

- Examples: oxycodone, hydromorphone
- Pros:
  - Potent analgesics
  - Commonly prescribed
- Cons:
  - Addiction potential
  - May not alleviate neuropathic pain well
  - Not ideal for elderly patients given side effect profile

Neuropathic Analgesics

- Examples: duloxetine, amytriptyline, gabapentin, pregabalin
- Pros:
  - Oral agents
  - Readily available
- Cons:
  - Maximal effect may take days to weeks to achieve for tricyclic antidepressants (TCAs), but faster for duloxetine
  - CNS depression
  - Use TCAs with caution in patients with psychiatric illness, especially if the patient is young

Invasive Approach

- Nerve Block
  - Pro:
    - Provide longer-lasting relief for neuropathic pain
  - Con:
    - More invasive

Summary 2

- Symptomatic treatment options
  - OTC analgesics
  - Bone pain vs neuropathic pain vs both
    - Topical applications (lidocaine patch or cream, fentanyl patch)
    - Neuropathic analgesics
    - Opioids
    - Nerve blocks
- The importance of keeping an open mind

Case Epilogue

- Started gabapentin 100 mg PO TID
  - Two days later, patient called back noting nausea, abdominal cramping, sweating, and unexplained anger/agitation
- Next we trialed ibuprofen 600 mg PO q6h ATC as a bridge to considering neuropathic analgesics (duloxetine)
  - Patient functional within 24 hr, though discomfort not completely resolved

Case Epilogue (cont)

- Patient ultimately changed jobs, after which her discomfort subsided
- CT chest 17 months after SBRT showed fractures in the left third and fourth ribs near the treatment area
  - PET/CT one month later did not suggest recurrence
  - Musculoskeletal changes stable on imaging in 2017
- Pain improved by follow-up 27 months after SBRT with intermittent remission and ongoing management with hydrocodone-acetaminophen 7.5/325 as needed
  - Managing physical activity at a new job but continuing to work