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

Plan Parameters for Chest Wall

$V_{30}: 17 \text{ cc}$

$D_{2 \text{ cc}}: 56.1 \text{ Gy}$

$D_{30 \text{ cc}}: 24.4 \text{ Gy}$

$D_{70 \text{ cc}}: 17.5 \text{ Gy}$

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 $\geq 20$ 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)

- 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 $D_{70 \text{ cc}}$, $D_{30 \text{ cc}}$, $D_{2 \text{ cc}}$, and $D_{\text{max}}$ 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
  - $D_{30 \text{ cc}}$ and $D_{70 \text{ cc}}$ 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, amitriptyline, 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