Role of RT in myeloma

What we know and what we don’t know

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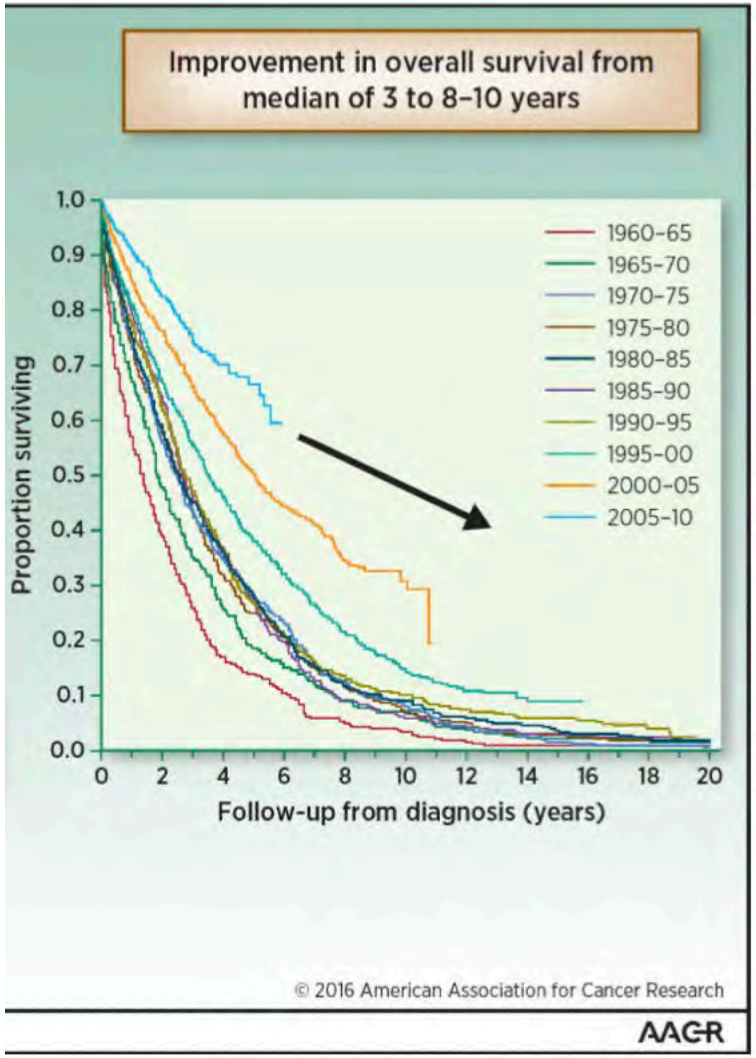
Disclosure

- Employer: University of Washington
- I have no conflicts of interest to disclose

Myeloma: Incurable, but treatable

Improved survival over time (median OS 10.5 y)

- By cytogenetics:
  - High-risk >6 y
  - Standard risk >12 y



Anderson Clin Cancer Res 2016, Joseph JCO 2020

Myeloma: Incurable, but treatable

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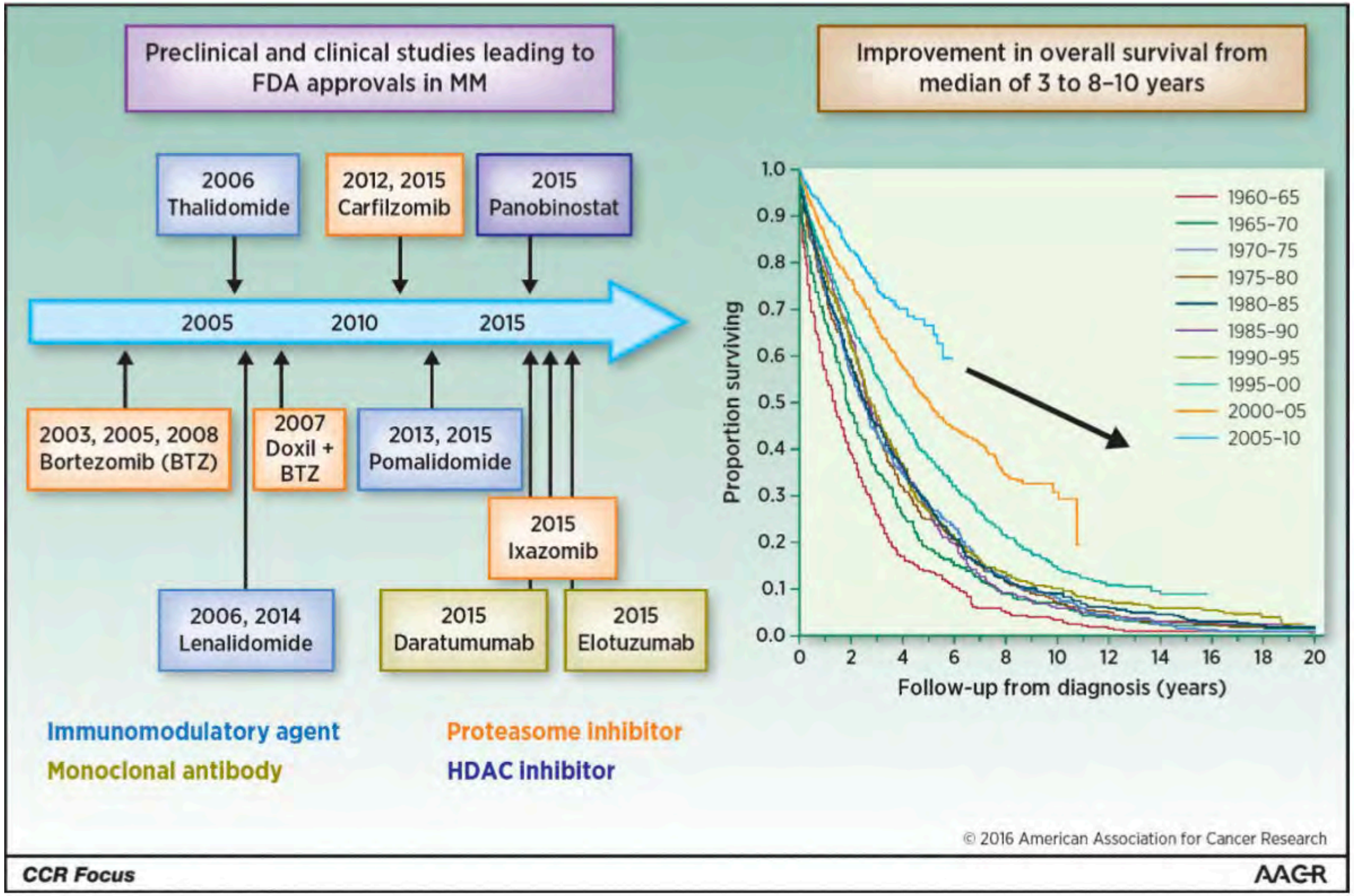
Myeloma ≠ Bone mets from solid tumor

Unique goals for an incurable cancer: achieve a response, prevent skeletal events, and with minimal toxicity



Anderson Clin Cancer Res 2016, Joseph JCO 2020

Role of RT for myeloma

Palliation of symptoms

- Uncomplicated bone (pain)
- Complicated bone
  - Compression of spinal cord, cauda, or nerve
  - Impending or path fracture
  - Prior surgery/RT
- Non-solitary plasmacytoma

Prevention

- Recalcification
  - ↓ fracture risk
- Local control
  - ↓ pain recurrence
  - ↓ neurologic complication risk

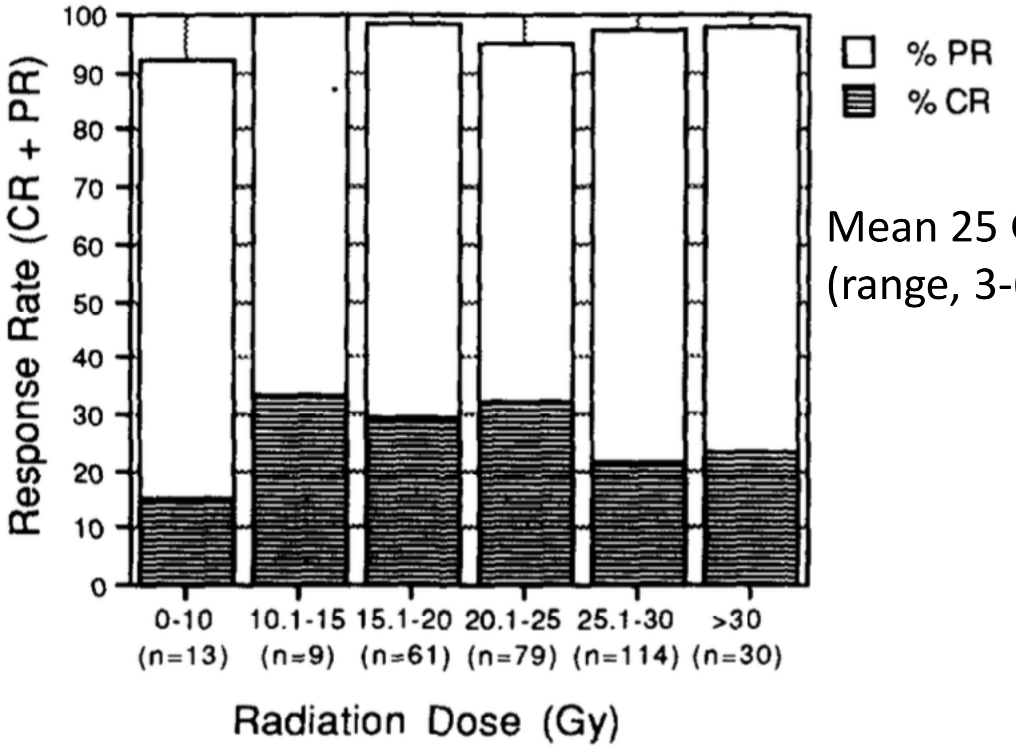
Bridging

- Palliate symptoms
- Prevent functional decline
- ?Augment immune response (priming)

Within the era of novel agents, RT still has many roles in myeloma management

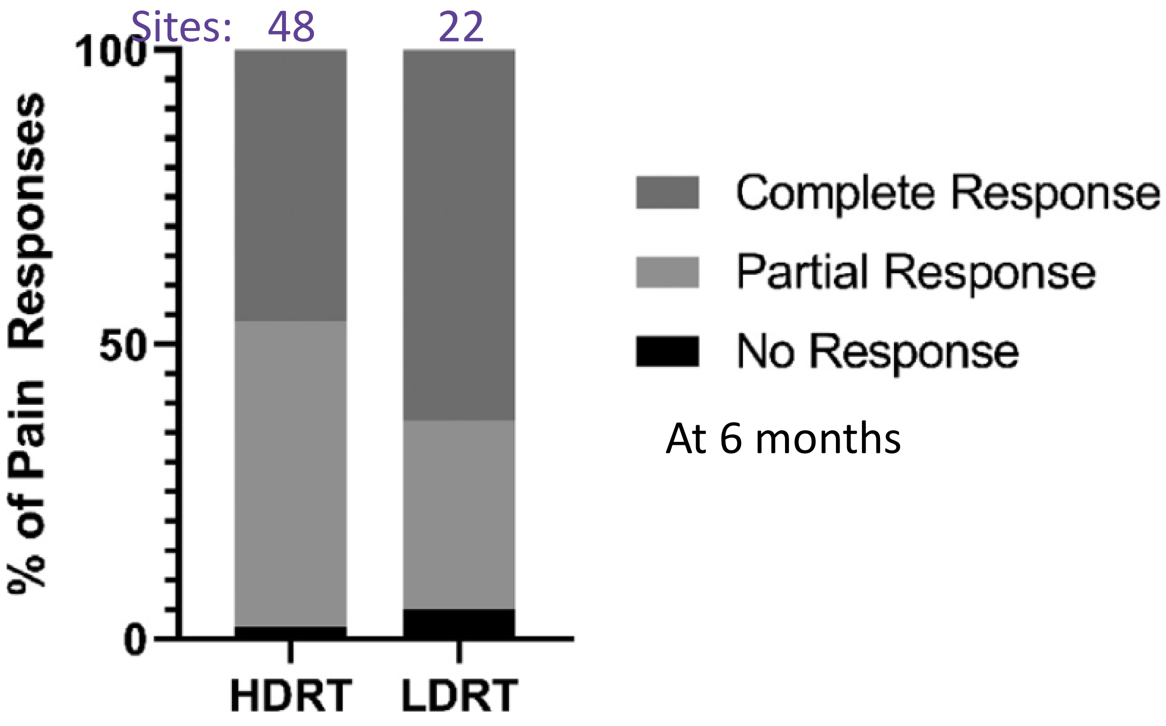
Palliation of pain with low RT dose

University of Arizona, 1975-1990
- 101 patients (316 sites)



Mean 25 Gy
(range, 3-60)

Duke/Durham VA, 2013-2019
- 35 patients (70 sites – all uncomplicated bone)



At 6 months

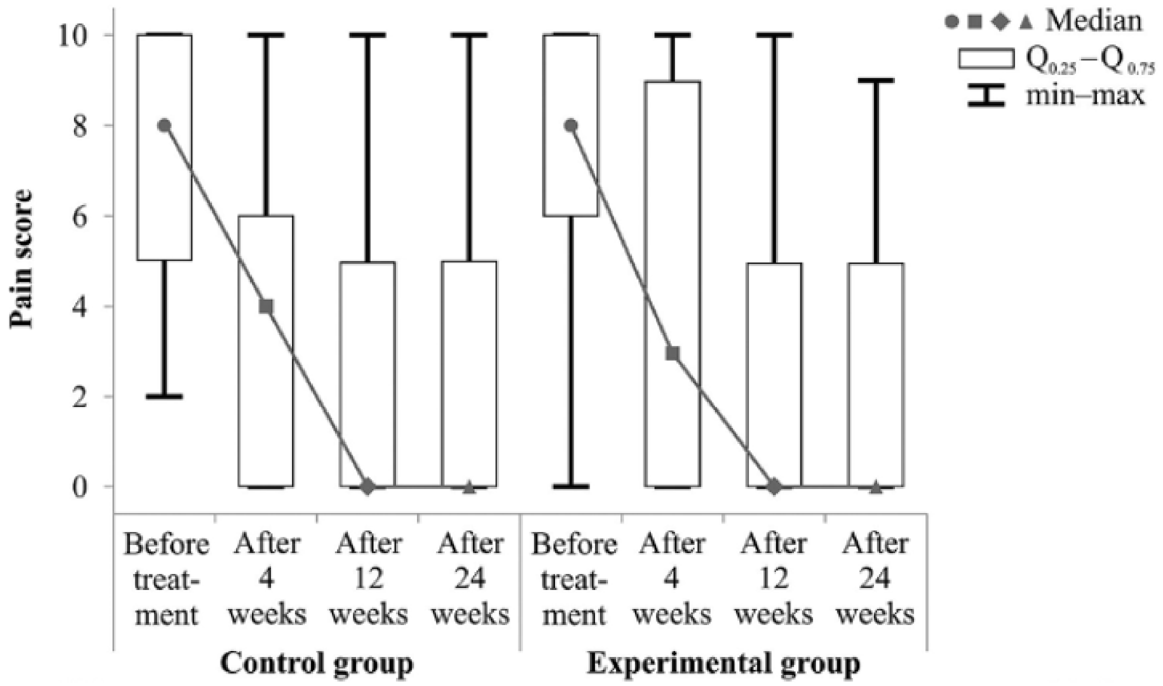
Doses as low as 10-12 Gy may achieve pain response

Leigh IJROBP 1993, Price ARO 2021

Do higher RT doses improve pain response?

Lithuanian University, 2010-2015

- Phase 3: 30 Gy/10 vs 8 Gy/1
- Included complicated lesions (e.g. 21% surgery)
- No difference in response
  - ORR: 84.5% (30 Gy) vs 74.4% (8 Gy)
  - CR: 69.4% vs 68.8%
- 4-wk QoL (EORTC QLQ-C30) improvement only with 30 Gy
  - More young patients (<65 y), new dx



30 Gy/10   8 Gy/1

How low can we go to palliate pain?

Ongoing ILROG collaborative study (NCT03858205)

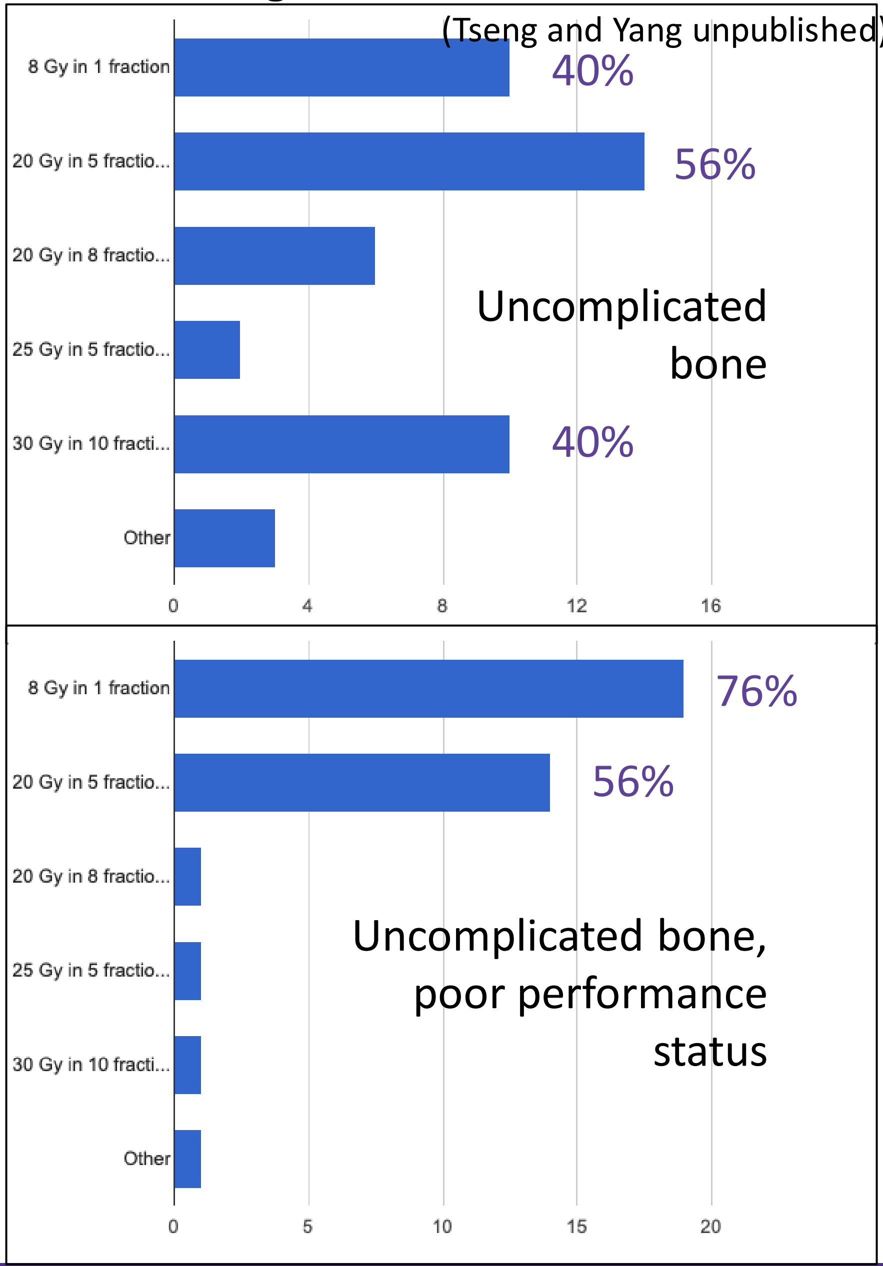
- PI: Dr. Leslie Ballas
- Phase 2, multi-institutional study of 4 Gy/1-2 fx
- Uncomplicated bone lesions
- 45 out of 65 accrued (7/2023)
- Planned interim futility analysis after 40 patients
  - Pre-specified: CR+PR ≥55%
  - Best response: CR 48%, PR 38%
- Supports continuation of trial

ILROG Manchester meeting 2023 (personal communication, Dr. Ballas)

Palliation of bone pain

- Range of effective doses (e.g. 8-30 Gy)
  - ORR 75-90%
  - Mechanism of response may involve non-tumor effects
  - Dose response seen in some but not all series → heterogeneity of lesions (e.g. complicated vs not)
- Rates of retreatment (~<10%)
  - Higher with BED ≤28 vs >28 Gy: 3.25% vs 1.83%

ILROG steering committee members, n=23



Mill Cancer 1980, Lee Radiat Oncol J 2016, Elhammali Hematologica 2020

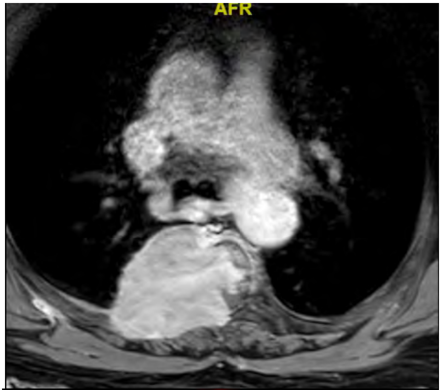
Palliation of bone pain

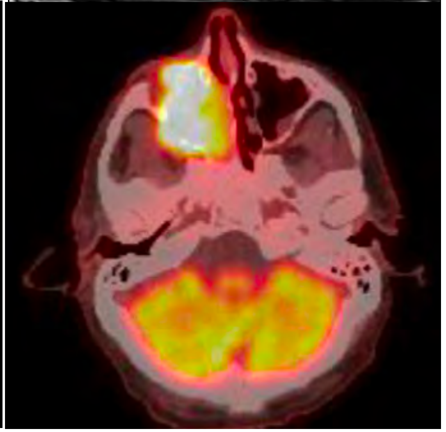
Dose-response for durability?

	N	**Median RT dose** (range)	**Outcome**
University of Arizona* *Leigh IJROBP 1993*	101 pts 316 sites	Mean 25 Gy (3-60)	Dose not associated with probability or time to relapse
Kyungpook National University Hospital* *Lee Radiat Oncol J 2016*	51 pts 87 sites	21 Gy (12-40)	In-field failure 16.3% ($EQD2_{10}$ ≤23.3 Gy) vs 9.5% (>23.3; p=.35)
Mount Sinai* *Wang PRO 2019*	130 pts 266 sites	20 Gy (2-40)	Pain recurrence (vs <20 Gy) 20- <30 Gy (HR 0.36, 0.14-0.94, p=.037) ≥30 Gy (HR 0.43, 0.15-1.25, p=.12)
MDACC* *Elhammali Hematologica 2020*	82 spine sites	Only 4 treated to ≥30 Gy	Radiographic spine LC BED (≤ or >28 Gy) HR 0.99 (0.87-1.13; p=.68)
Duke/Durham VA *Price ARO 2021*	35 pts 70 sites	HDRT 20 Gy vs LDRT 4 Gy	No difference in duration of pain response HDRT vs LDRT (p=.91)

*Included complicated bone lesions

RT palliation of soft tissue disease





Includes:

- Cord/cauda compression
- Nerve root compression
- Non-solitary plasmacytoma

Palliation likely requires adequate shrinkage of tumor

- Several unknowns:
  - Role of spine decompression?
  - Dose for response?
  - Dose for control?
- University of Arizona: similar doses used for pain may be effective for soft tissue

Table 3. Mean dose and response rate by symptom

Symptom	Mean dose (Gy)	Response rate (CR + PR/total)
Pain	25.3 ± 7.4	97% (288/296)
Palpable mass	25.4 ± 3.4	100% (7/7)
Neurological impairment	28.2 ± 4.5	90% (18/20)

Leigh IJROBP 1993

RT alone for cord/cauda compression

Retrospective series	**University of Lubeck** (n=238)
Presence of neurologic sxs	100% (motor deficit)
RT dose	Short (8 Gy/1, 20 Gy/5) Long (30 Gy/10, 37.5 Gy/15, 40 Gy/20)
Response	~1 month: • 53% improved motor function • 44% stable • 64% of non-ambulatory (n=44) regained ability to walk
Other outcomes	• Local control (3-yr): 69% (short) vs 90% (long course; p=.29)

Rades Radiol Oncol 2016, Zijlstra J Bone Joint Surg Am 2023

RT alone for cord/cauda compression

Retrospective series	**University of Lubeck** (n=238)	**MGH/Netherlands** (n=162)
Presence of neurologic sxs	100% (motor deficit)	38% (motor and/or sensory deficit) 100% Bilsky grade 2 or 3
RT dose	Short (8 Gy/1, 20 Gy/5) Long (30 Gy/10, 37.5 Gy/15, 40 Gy/20)	30 Gy/10 most common (37%)
Response	~1 month: • 53% improved motor function • 44% stable • 64% of non-ambulatory (n=44) regained ability to walk	12-24 months: • 10% improved • 73% stable • 16% of those neuro intact at baseline deteriorated (17% overall)
Other outcomes	• Local control (3-yr): 69% (short) vs 90% (long course; p=.29)	• 12% with additional treatment (RT, surgery) ≤90 days • Dose not associated with neuro outcome

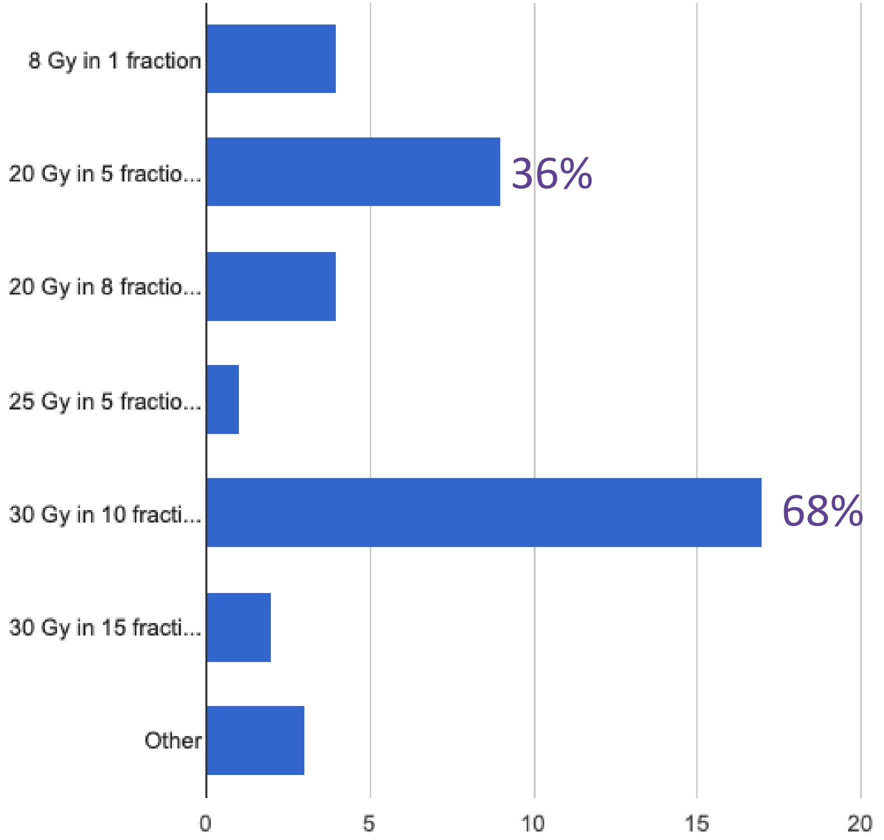
Are there a subset of patients that may benefit from more therapy beyond RT alone?

Rades Radiol Oncol 2016, Zijlstra J Bone Joint Surg Am 2023

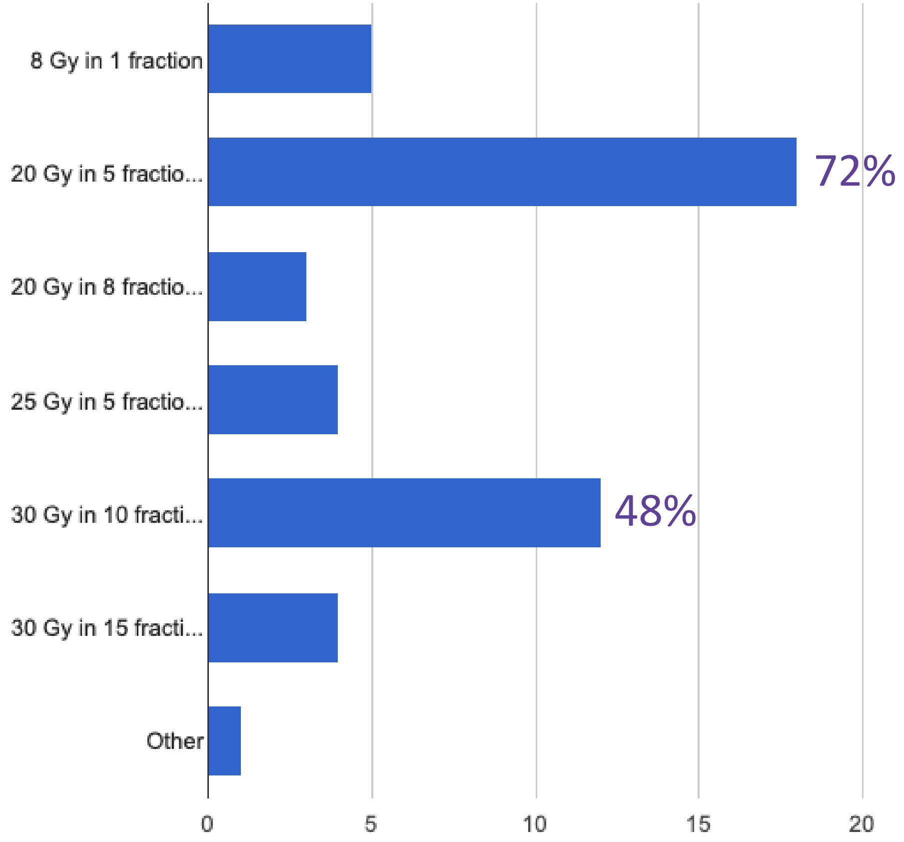
RT palliation of soft tissue disease

Survey of ILROG steering committee members

Cord compression, good prognosis



Symptomatic, non-solitary plasmacytoma



Tseng and Yang unpublished

Sometimes RT alone is not enough …

Surgical decompression
- Bony retropulsion into spinal canal
- Prior RT limiting re-RT dose

Stabilization of impending/path fracture
- Long bone (Mirels' criteria)
- Spine (SINS score) – fusion, vertebral augmentation
- *Addresses pain from mechanical instability and improve bone healing (long bone)*

Post-operative RT

Recommended unless oncologic resection performed

- No data in myeloma (e.g. Townsend IJROBP 1995)

Dose

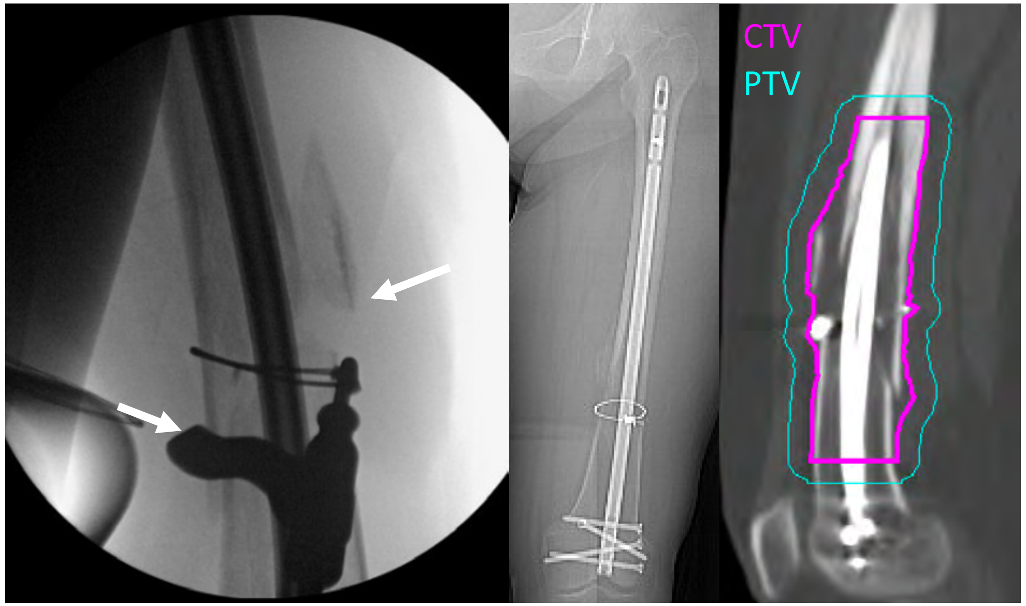
- Higher RT dose may delay/prevent callus formation necessary for bone repair (animal models)
- Stabilization of bone (e.g. pinning) ≈ callus formation
  - → Theory: higher doses (e.g. 20-30 Gy) should not impair healing in a stabilized bone
  - Observed: BED≥30 Gy did not interfere with healing (7 fracture sites)
- Optimal dose unknown
  - MDACC: Median BED 25 Gy_{10} (11.7-46.9) associated with 2 in-field recurrences (40 sites)
  - Dose not associated with local failure (continuous BED, HR 0.82 (0.60-1.11))

Cooley Am J Anat 1958, Elhammali CLML 2019, Meredith ARO 2023

Post-operative RT target

GTV (+/- 1-2 cm along bone)
Do not need to chase entire hardware

- Low rate of recurrence within same bone
  - 4 of 41 irradiated limbs (NYU)
  - Median 27.8 Gy to GTV+1-2 cm
- Low rate of recurrence when hardware not fully covered
  - 5 of 40 sites (12.5%) (MDACC)
  - Median 80% of hardware covered (28-100%)
  - Median BED 25 Gy_{10}



- 2-2.5 cm margin along bone from fracture as no pre-fracture imaging and GTV difficult to appreciate

Catell IJROBP 1998, Elhammali CLML 2019

RT for prevention of skeletal events

Recalcification

University Hospital Gemelli, 1996-2007

- N=52 MM or SP
- Median RT 38 Gy (range, 16-50)
- 42 evaluated for recalcification (X-ray, CT)
  - Achieved at median 6 mo (3-14)
  - CR 38%, PR 12%

Improved spine stability

University Hospital Heidelberg, 2006-2016

- N=130 MM treated to spine
- Median RT 30 Gy (range, 20-40)
- Unstable lesions (Taneichi scoring system)
  - 51% (before RT), 41% (3 mo), 24% (6 mo)

Reduction vertebral fractures

University of Louvain, Brussels

- N=12 prospectively followed by MRI after spine RT (30-40 Gy/15-20)

	Radiated VB (n=57)	Unirradiated VB (n=147)
Fracture	5%	20%
New focal marrow lesion	4%	27%

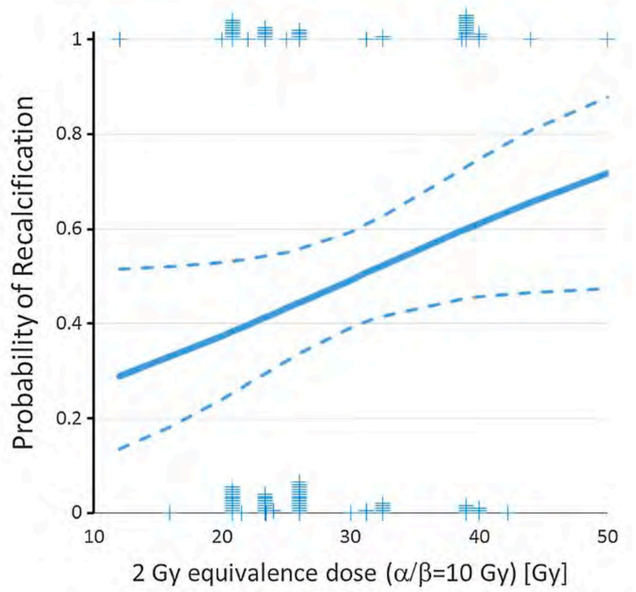
Recalcification of bone after RT may improve bone stability and risk of fracture in spine

Lecouvet Br J Haematol 1997, Balducci Strahlenther Onk 2011, Lang CLML 2017

Recalcification: Is there a dose response?

	N	RT dose	Outcome
Heinrich-Heine-University Dusseldorf *Matuschek Radiat Oncol 2015*	81 pts 108 sites	Median 25 Gy/10 fx (range 8-50)	• CT and/or MRI (3 mo-1 yr after RT) • 48% overall recalcification (CR 23%) • Higher dose associated with better overall recalcification
Lithuanian University *Rudzianskiene Strahlenther Onkol 2017*	101 pts	8 Gy/1 vs 30 Gy/10	• Bone X-ray eval (94.1% pts) • 33.7% overall recalc (CR 18%) • No difference by dose

Heinrich-Heine-University Dusseldorf



Limited data whether dose-response exists

Likely requires prospective studies with radiographic follow-up

Individualizing RT dose along a patient's course

My clinical practice

Systemic therapy

Diagnosis	Relapse #1	Relapse #2	Relapse #3	Relapse #4	Relapse #5

Diagnosis:
- Induction therapy
- (Stem cell transplant)

Relapse #1–#3:
- Anti-CD38 mAb (e.g. daratumumab)
- Lenalidomide
- Pomalidomide
- Bortezomib
- Carfilzomib

Relapse #4–#5:
- Anti-BCMA (e.g. CART, bi-specific)
- Alkylator containing agents
- Clinical trials

Radiotherapy

- 20-30 Gy
- Smaller fraction sizes (e.g. 2.5-3 Gy/fx)
- *Goals: durability (e.g. spine), prevent skeletal events, minimize toxicity*

→

Dose/fx influenced by site, lesion type, disease burden, performance status, concurrent systemic therapy

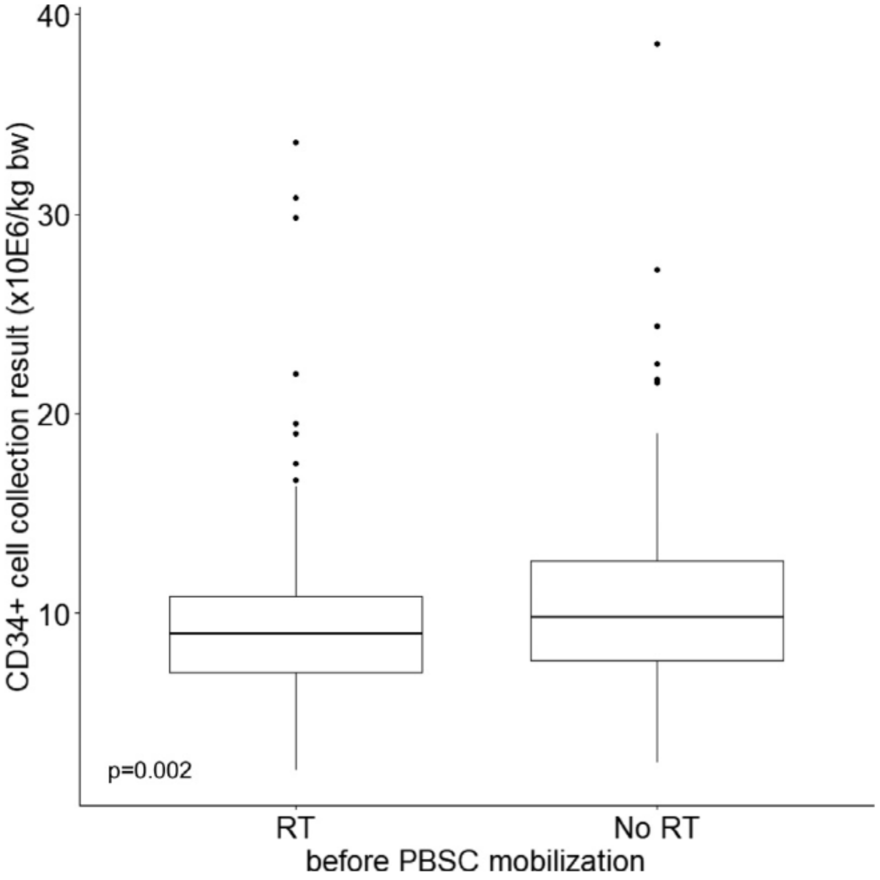
- 8-20 Gy
- More hypofractionated fractions (e.g. 4-8 Gy/fx)
- *Goal: limit time on treatment*

Safety with systemic therapy

Stem cell transplant

RT prior to stem cell transplant

- No difference in collection failures with RT prior to stem cell mobilization (11%) vs not (6%)
- RT patients required higher # leukapheresis sessions to reach collection goal
- No correlation between CD34+ yield, volume of irradiated bone marrow or EQD2



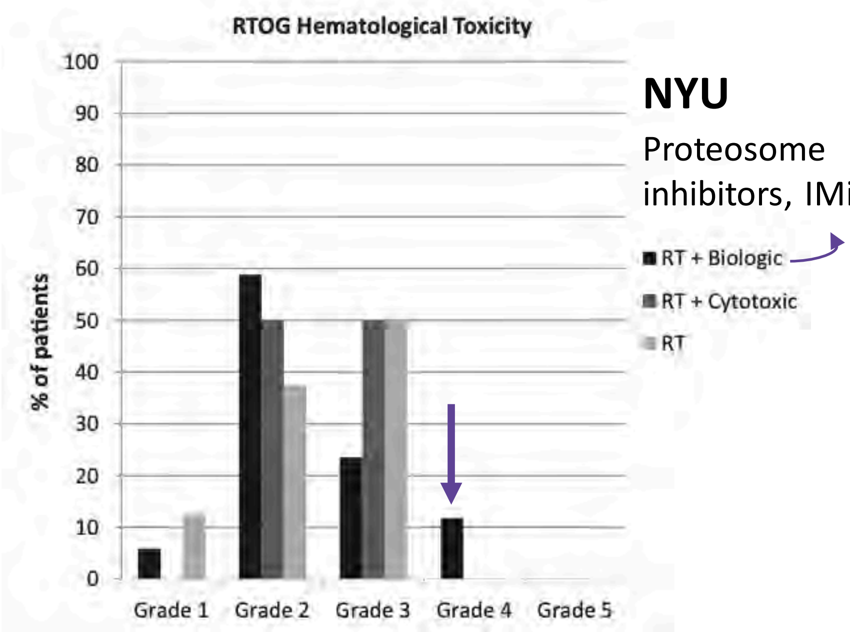
Safety with systemic therapy

Novel agents

Lenalidomide

- N=19 SP prospectively irradiated concurrently with len/dex
- NS higher heme tox (any grade) for RT+len vs RT alone
  - Thrombocytopenia: 10.5% vs 0% (p=.10)
  - Neutropenia: 15.8% vs 3.7% (p=.18)

Proteosome inhibitors (PI)/IMiDs



NYU

Proteosome inhibitors, IMiDs

- Similar findings for PI (University Hospital Muenster), especially for thrombocytopenia
- No difference in lab values RT vs RT+ST (Mount Sinai)

Caution with RT concurrent with proteosome inhibitors

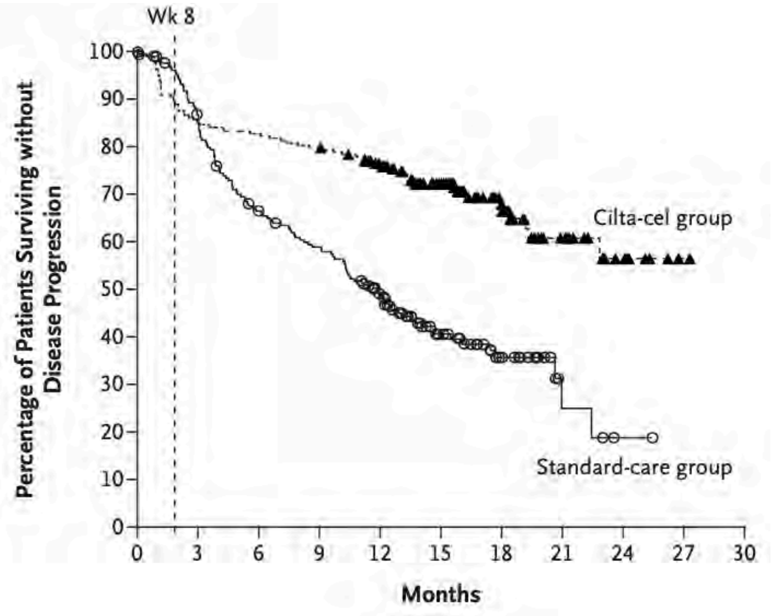
- *Consider holding PI or decreasing dose/fx*

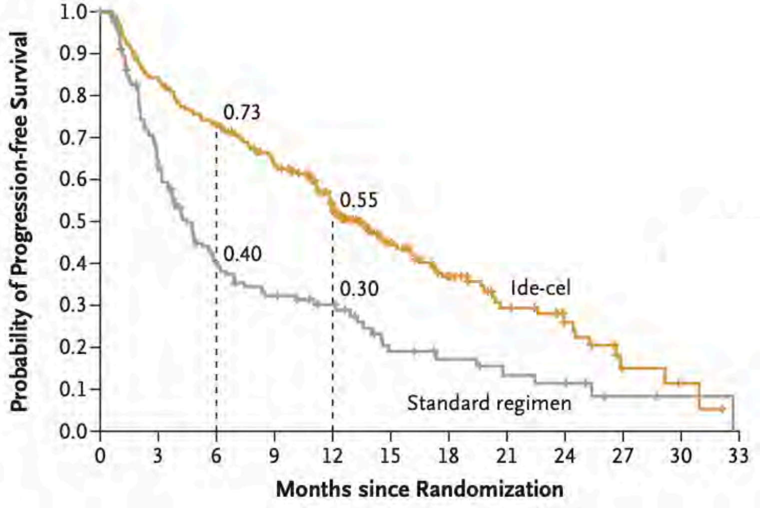
Shin CLML 2014, Mignot IJROBP 2020, Oertel Cancers 2023

Bridging RT for CAR-T cell therapy

Anti-B cell maturation antigen (BCMA) CAR-T

- Approved for r/r MM ≥4 lines systemic therapy
  - Unclear whether remissions are durable (c.f. LBCL)
- Role of RT
  - Palliate/prevent symptoms → maintain/improve performance status
- Optimal dose not known
- Consider delaying RT until after leukapheresis, especially if concerns for lymphopenia
  - Lower *in vitro* proliferation during manufacturing with RT <1 year and <100 days before apheresis (U Penn)
- Bridging RT appears safe
  - No difference with *in vivo* CART expansion (U Penn)





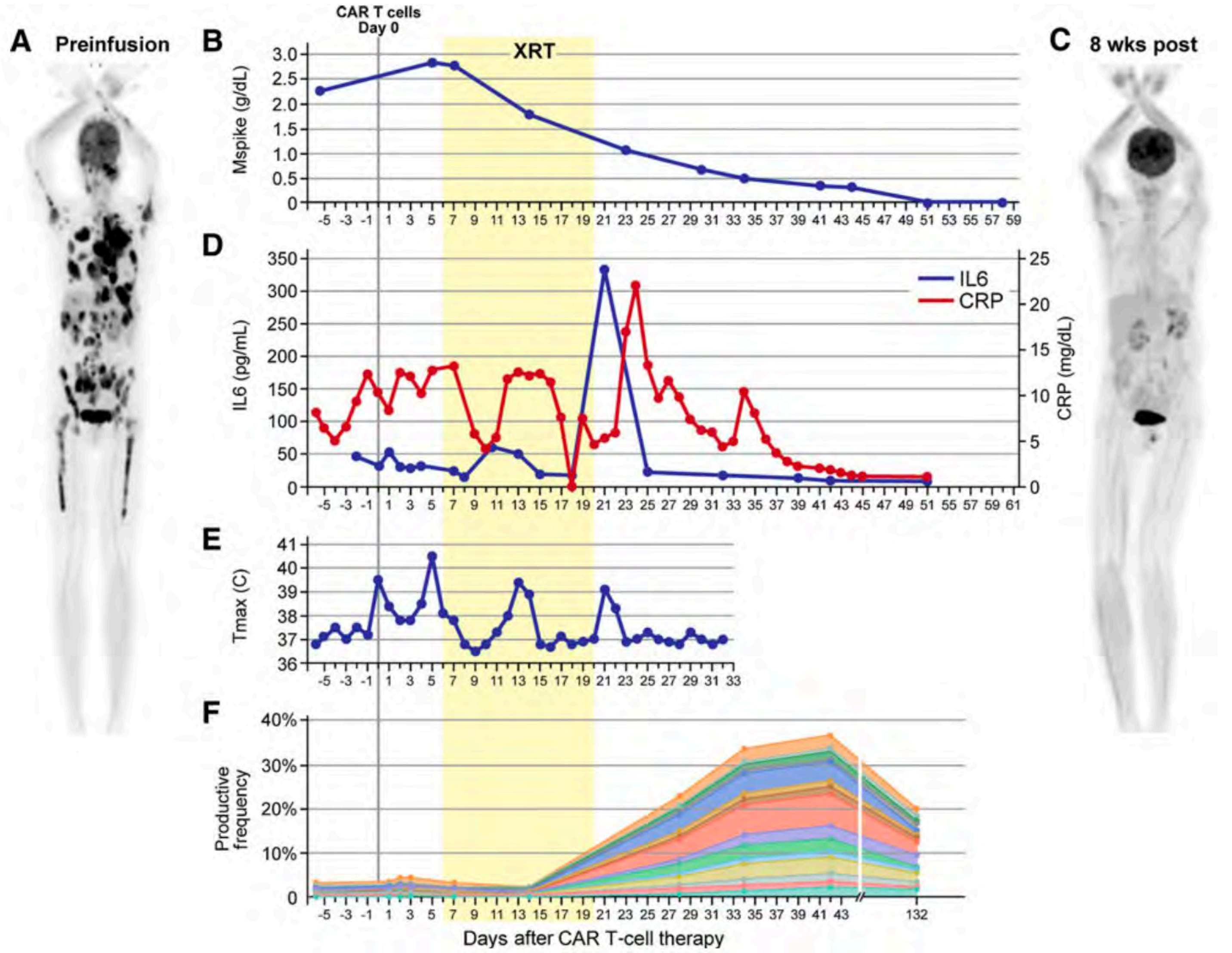
Manjunath Clin Cancer Res 2021, Rodriguez-Otero NEJM 2023, San-Miguel NEJM 2023

Bridging RT for CAR-T cell therapy

Potential RT – CART synergism?

- 63F enrolled CART clinical trial
- RT for cord compression (T1-T8, 20 Gy/5) → C2-WBRT (20 Gy/5)
- IL6/CRP: Markers of CAR T-cell mediated CRS
- Increase in T-cell receptor diversity after RT

Session 7: CAR-T and new treatments later this afternoon



Smith Cancer Immunol Res 2019

Summary

- RT is an effective modality for palliation of myeloma, including pain, cord/nerve compression, and plasmacytomas
  - *Excellent pain response with low RT doses*
  - *With improving survival, interest in other endpoints: local control, re-calcification, prevention of skeletal events → unknown if higher doses are needed*
  - *Future studies: clear inclusion criteria, categorization of lesions (complicated vs uncomplicated), radiographic follow-up*
- Though myeloma is a radioresponsive disease, surgical intervention should be considered for impending/path fracture, bony retropulsion
  - *Role of surgery for cord compression is unknown – are there a subset of patients that may benefit?*

Questions