Best Practices for Palliative Radiotherapy

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Parts 1 and 2 Objectives

1. Understand and perform the radiation oncologist's role in palliative oncology care, according to national guidelines (ASCO, Choosing Wisely, ASTRO Bone Mets Guidelines, National Consensus Project)
2. Understand and apply in patient care key palliative care skills, e.g., prognostication, pain management skills
3. **Understand and apply the evidence-based management principles to common palliative scenarios: uncomplicated and complicated bone metastases, reirradiation principles, palliation in head and neck cancers**

For help with the CME questions, look out for the leap year frog…

Part 2. Evidence-Based Approaches to Common Clinical Scenarios

Tracy A. Balboni MD, MPH, FAAHPM

Part 2. Evidence-based management principles in common palliative scenarios

- Uncomplicated and complicated bone metastases
- Reirradiation principles
- Palliation in malignancies of head and neck

Complicated/Uncomplicate Mets: Scenario 1

- 59 yo M PS 1 with met adenocarcinoma of unknown primary after presenting with T6 cord compression (pain only). Staging: widespread bone, lung, nodal, liver metastases, including small R humerus met
- Undergoes spine decompressive surgery→ RT 3Gy x 10
- Completes RT and about to start chemotherapy, notes 6/10 right arm pain
- MRI: 3cm met in proximal diaphysis of right humerus

Case questions

1. How to define complicated vs uncomplicated bone metastases?
2. How to determine risk of pathological fracture?
3. Best fractionation scheme for RT when concern for fracture?

1. Complicated versus Uncomplicated

- Uncomplicated Bone Metastases:
  1. No pathological (some also use impending) fracture
  2. No cord compression (some use early MSCC and/or nerve root compression)
  3. No prior radiation therapy
- Why uncomplicated vs complicated important?
  - SF versus MF trials apply to uncomplicated bone metastases
  - Do have dedicated trials for reirradiation, spinal canal compression which are better applied to complicated setting, scant data in post-surgery long bone setting

Is Case 1 complicated bone met? How do we determine impending fracture risk?

Key Evidence: Mirel's Criteria Fracture Risk

Score	1	2	3
Site of lesion	Upper limb	Lower limb	Trochanteric region
Size of lesion	<⅓ of bone diameter	⅓-⅔ of bone diameter	>⅔ of bone diameter
Nature of lesion	Blastic	Mixed	Lytic
Pain	Mild	Moderate	Functional

Score	Fracture risk*	Recommendation
≤7	0-4%	Safe to irradiate with minimal risk of fracture
8	15%	Consider prophylactic fixation
≥9	>33%	Prophylactic fixation indicated

Mirels H. Metastatic disease in long bones: A proposed scoring system for diagnosing impending pathologic fractures. 1989. Clin Orthop Relat Res. 2003 Oct;(415 Suppl):S4-13.

Key Evidence: Spinal Instability Neoplasia Score

Assessment of Spinal Stability with SINS, includes

6 factors, summed to obtain score:

- 0-6 stable
- 7-12 intermediate
- 13+ unstable

Table 1. SINS

SINS Component	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
Pain*	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements†	
Bilateral	3
Unilateral	1
None of the above	0

Fourney et al. *JCO* 2011

Case continued

- Pt seen by orthopedic surgeon, discussion with med onc, rad onc, given chemotherapy urgency and modest risk of fracture, RT alone
- What fractionation?

Dutch Bone Metastases Trial

Study Description

- RCT pts w/ bone mets (all except RCC/melanoma): 8Gy x 1 vs. 4Gy x 6
- Ineligible:
  - Prior RT
  - Path fractures (impending fracture were ELIGIBLE)
  - MSCC
  - Cervical spine mets
  - RCC and melanoma

Steenland et al. *Rad Onc, 52;* 1999

Dutch Bone Metastases Trial

Results

- N=1171 pts
- Acute side effects: ND in SF/MF
- Pain CR+PR: ~71% in SF/MF groups
- Retreatment: 25% (SF) vs. 7% (MF), $p<0.05$
- Path fractures: 4% (SF) vs. 2% (MF), $p<0.05$ (denominator is all bone sites treated, whether or not weight bearing)

DBMT: Analysis of Femur Path Fracture Cases

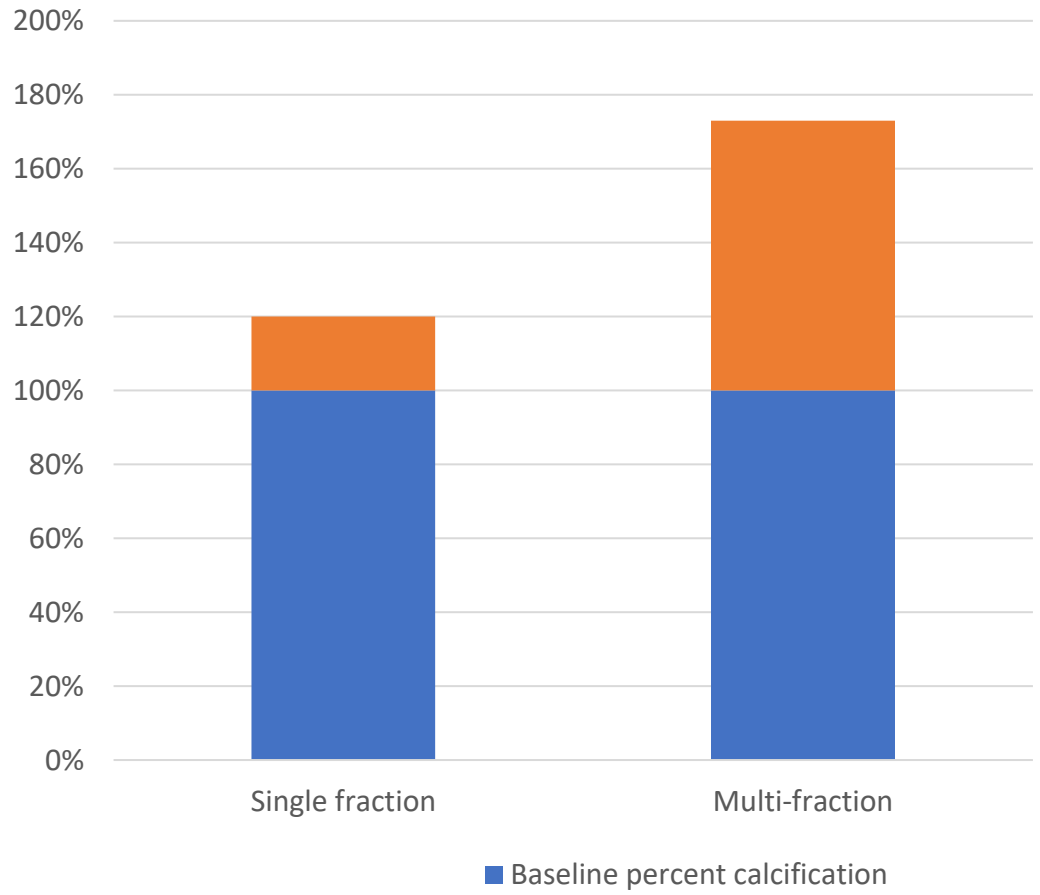
Results

- Of 1171 pts, 110 femur lesions with 14 fractures (13% rate)
- RFs examined: increasing pain, lesion size, circumferential cortical involvement
- Key predictors of fx: size >3cm, circumferential cortical involve >50%

Van der Linden et al. *JBJS, 86 (4) 2003*

Bone Remineralization after RT

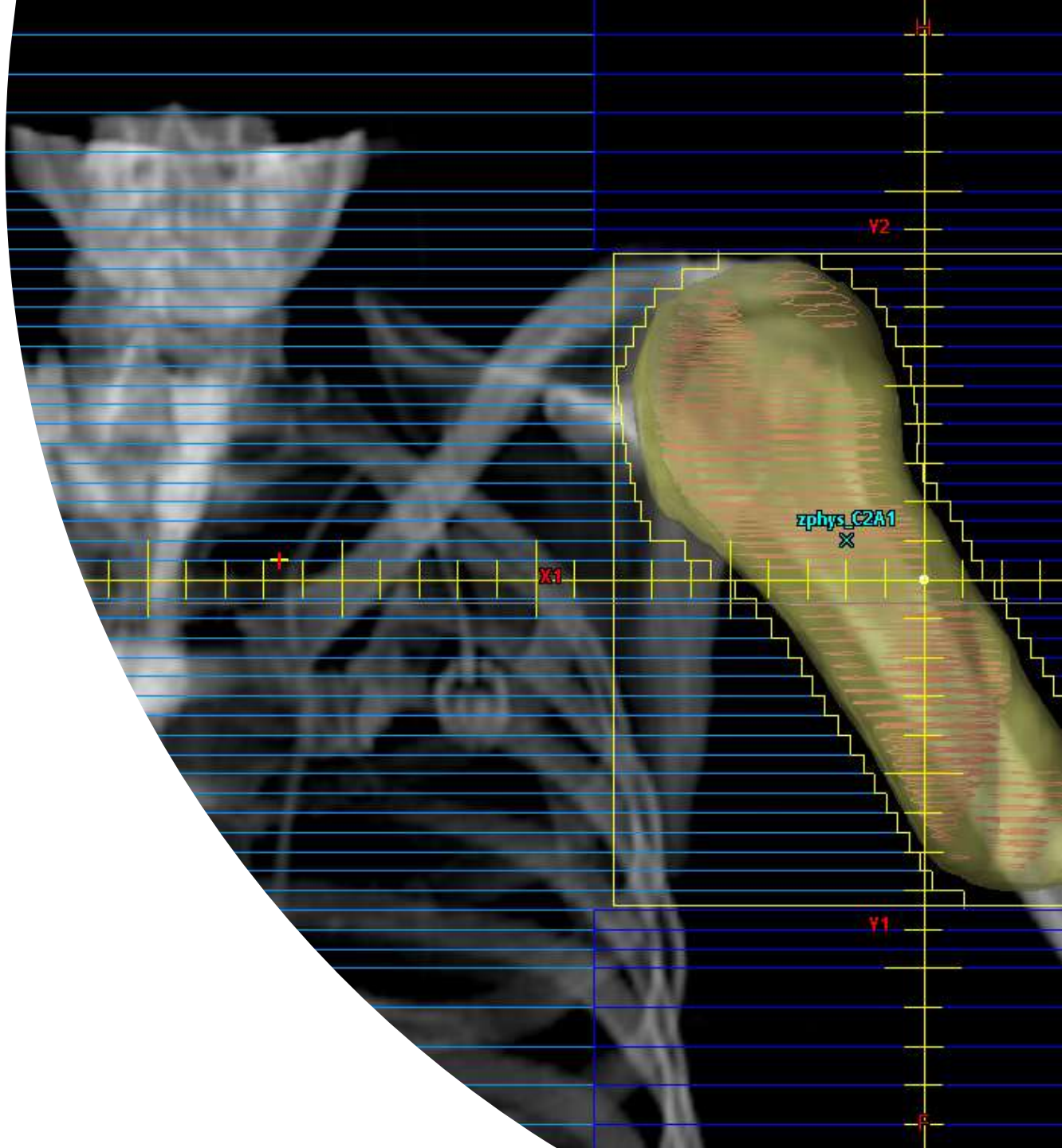
- RCT 170 bone mets pts (breast, lung, prostate or RCC): 8Gy x 1 vs. 3Gy x 10
- ND in pain ORR (78% SF vs. 81% MF)
- Recalcification (CT scan at 6 months): 120% (SF) vs. 173% (MF), p<0.001



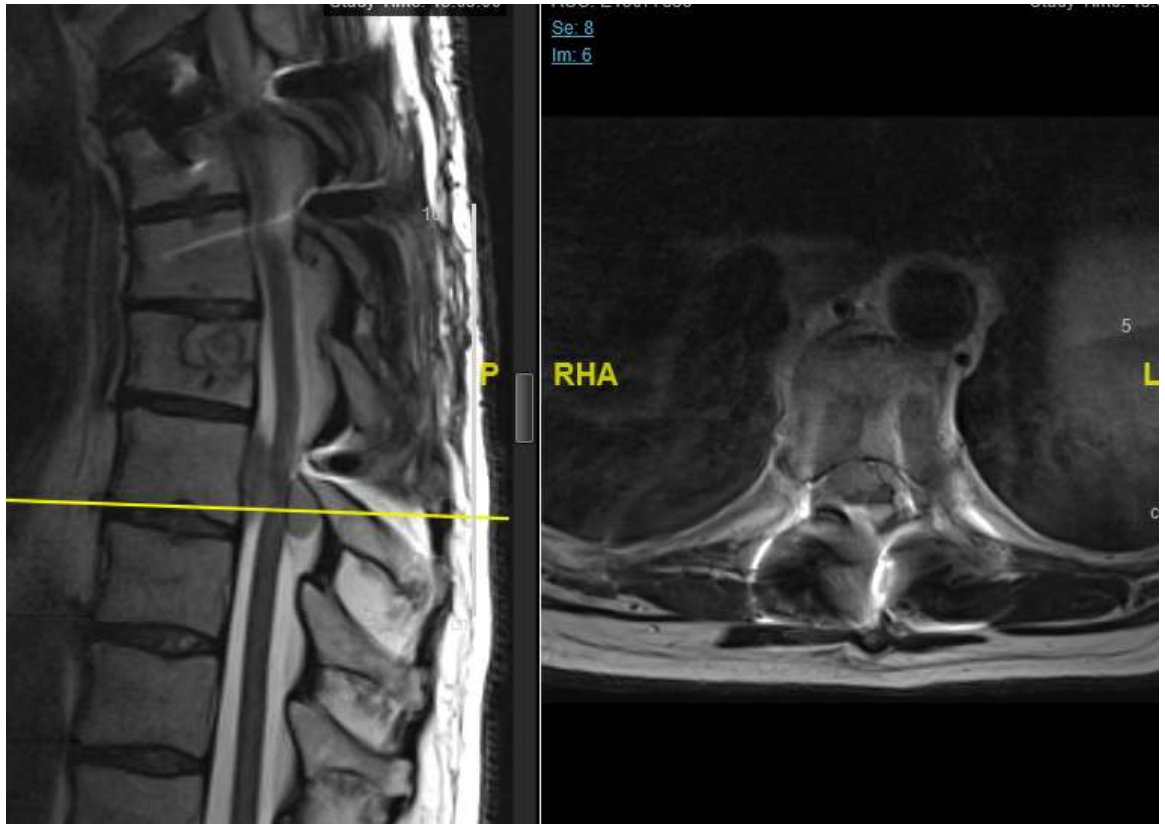
Koswig et al. *Strahlenther Onkol, 175 1999*

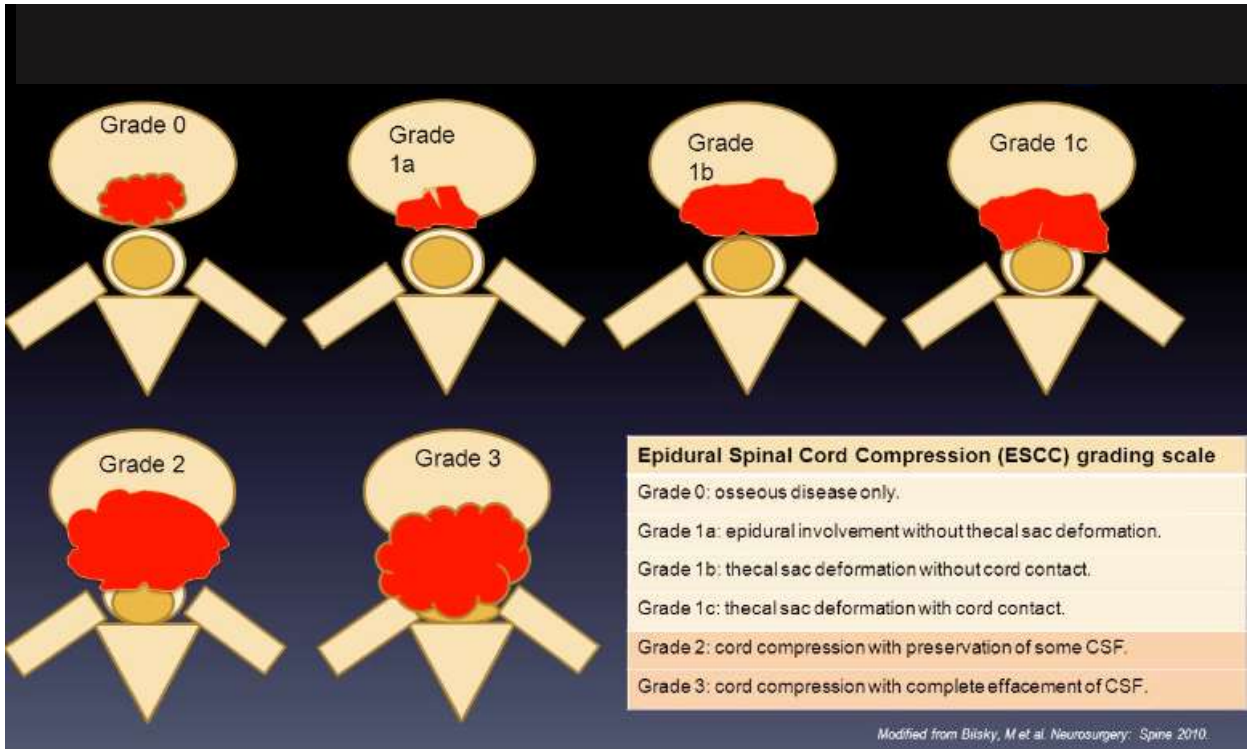
Recommendation

- RT plan 4Gy x 6 → chemotherapy
- Shoulder pain resolved
- 6 months later notes increasing mid back pain, worse while on treatment table and at night
- MRI spine performed



Scenario 2: Malignant spinal canal compression





MRI spine: severe (grade 3) T8 cord compression w/ complete effacement of CSF, **T8 included in prior RT**

CT restaging: Progression of disease, CT - no spinal instability at T8 (SINS 5)

Prognosis: Estimated to be ~6 months (per Chow et al *JCO* 2008)

Malignant Epidural Spinal Canal Compression (MESCC) "Gold Standard" Data

Patchell et al. *Lancet* 2005: RCT of surgery + RT vs. RT alone in 101 MESCC pts (RT: 3Gy x 10)

- Exclusion criteria: life expectancy ≤3 and/or not surgery candidates
- DID NOT exclude unstable spines: 35% RT alone; 40% surg+RT
- Greater ambulatory status after surgery+RT vs. RT alone (84% vs. 57%, p=0.001)
- Surg assoc w/ improved survival (med 126 vs. 100 dys, p=0.03)

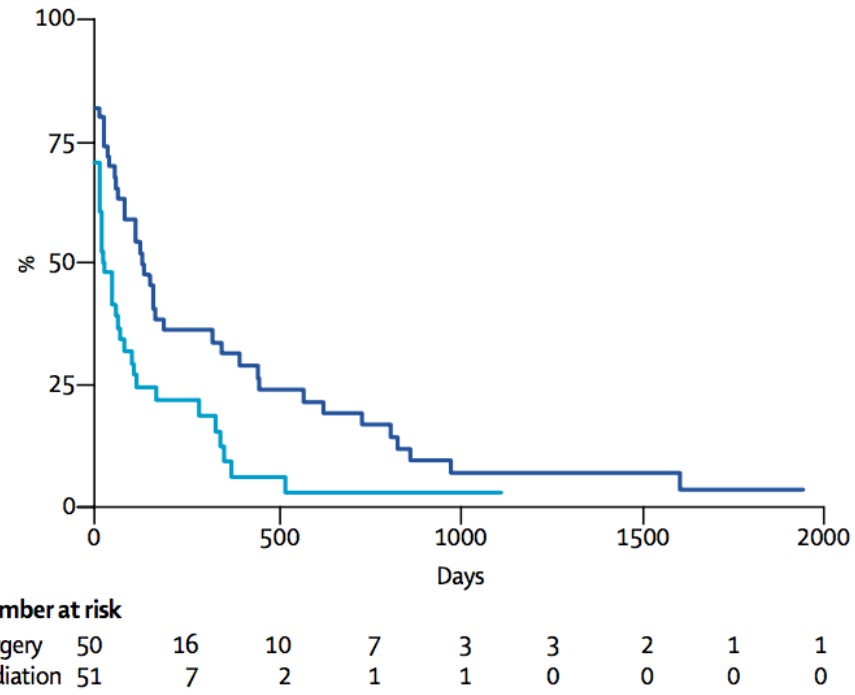


Figure. Kaplan-Meier estimates of length of time all study patients remained ambulatory after treatment

MESCC: Other Data Informing Role of Surgery

Rades et al. JCO 2010: Matched pair analysis of 108 surgery + RT pts vs. 216 RT alone pts

- Excluded pts with spinal instability
- Matching on 11 prognostic factors: age, gender, PS, primary tumor type, number of VBs involved, other bone mets, other visceral mets, interval from dx to MSCC, ambulatory status, time to developing motor deficits, RT regimen
- ND in ambulatory status post S+RT vs. RT alone (69% vs. 68%, p=0.99)
- ND in regaining ability to walk post S+RT vs. RT alone (30% vs. 26%, p=0.86)
- Limitations: may be residual selection bias

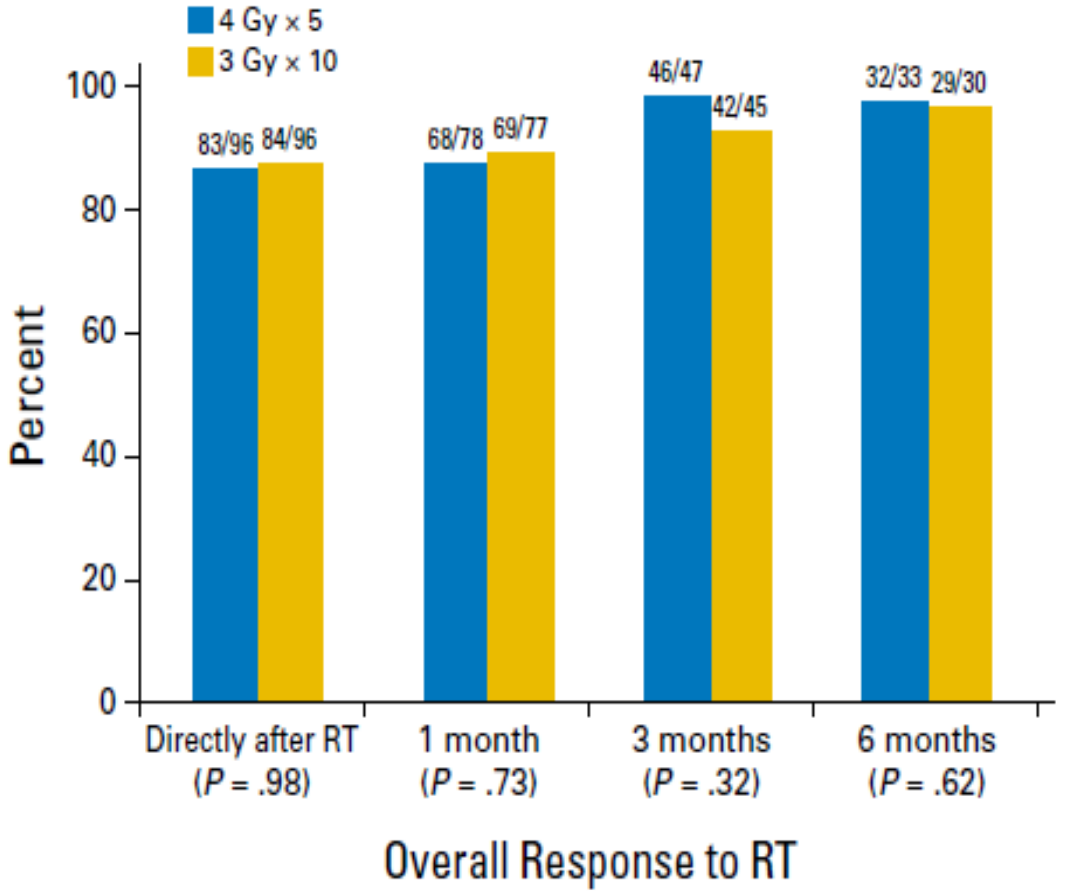
Rades et al. ***JCO, 28 (22), 2010***

MESCC: Hypofrac RT in Poor Prognosis

SCORE-2 Trial (Rades et al *JCO* 2016):

203 poor prognosis (est median LE 3 mo)
MESCC pts randomized to 4Gy x 5 vs 3Gy x 10

- No difference in ambulatory function (figure)
- Local PFS and OS at 3 and 6 months: no difference
- mOS for entire cohort was 3.2 months



Data on SFRT for MESCC

SCORAD III: *Hoskin et al. JAMA 2019*

Non-inferiority multicenter RCT in UK/Australia, 8 Gy/1 vs 20 Gy/5 for MSCC, primary endpoint ambulatory status at 8 weeks, within -11% non-inferior (in % with the ability to ambulate)

- 688 patients enrolled, 66% ambulatory pre-RT
- 8 Gy/1 vs 20 Gy/5 at 2mo: ambulatory status preserved in 69.5% vs 73.3%, 90% CI risk difference -11.85% to 4.28%
- Just missed reaching non-inferiority criteria

- Median OS for entire cohort ~3mo, no difference between arms

Principles of Spinal Re-RT

Nieder data (IJROBP 2004, 2005):

- 78 cases, 11 w/ radiation myelopathy (med 11 mos, range 4-25 mos)
- No RM cases seen w/ BEDGy2 ≤135.5
- RM cases seen w/ interval ≤2mos, BED individual course ≥102
- Risk scoring created based on BED (Gy2) each course, interval, cumulative BED

Factor	0 pts	1 pt	2 pts	3 pts	4 pts	5 pts	6 pts	7 pts	8 pts	9 pts
Cumulative BED Gy2	<120	120.1-130	130.1-140	140.1-150	150.1-160	160.1-170	170.1-180	180.1-190	190.1-200	>200
Interval<6mo					X (4.5)					
BED course ≥102Gy2					X (4.5)					

Group	Points	Myelopathy 2005 (1)	**Myelopathy updated**	% Myelopathy 2005 (1)	**% Myelopathy updated**
Low risk	≤3	0/24	**1/30**	0	**3**
Intermediate risk	4–6	2/6	**2/8**	33	**25**
High risk	>6	9/10	**9/10**	90	**90**

Cord Tolerance in SBRT Spine ReRT

CLINICAL INVESTIGATION

REIRRADIATION HUMAN SPINAL CORD TOLERANCE FOR STEREOTACTIC BODY RADIOTHERAPY

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Purpose: We reviewed the treatment for patients with spine metastases who initially received conventional external beam radiation (EBRT) and were reirradiated with 1–5 fractions of stereotactic body radiotherapy (SBRT) who did or did not subsequently develop radiation myelopathy (RM).

Methods and Materials: Spinal cord dose–volume histograms (DVHs) for 5 RM patients (5 spinal segments) and 14 no-RM patients (16 spine segments) were based on thecal sac contours at retreatment. Dose to a point within the thecal sac that receives the maximum dose (P_{max}), and doses to 0.1-, 1.0-, and 2.0-cc volumes within the thecal sac were reviewed. The biologically effective doses (BED) using $\alpha/\beta = 2$ Gy for late spinal cord toxicity were calculated and normalized to a 2-Gy equivalent dose (nBED = $Gy_{2/2}$).

Results: The initial conventional radiotherapy nBED ranged from ~30 to 50 $Gy_{2/2}$ (median ~40 $Gy_{2/2}$). The SBRT reirradiation thecal sac mean P_{max} nBED in the no-RM group was 20.0 $Gy_{2/2}$ (95% confidence interval [CI], 10.8–29.2), which was significantly lower than the corresponding 67.4 $Gy_{2/2}$ (95% CI, 51.0–83.9) in the RM group. The mean total P_{max} nBED in the no-RM group was 62.3 $Gy_{2/2}$ (95% CI, 50.3–74.3), which was significantly lower than the corresponding 105.8 $Gy_{2/2}$ (95% CI, 84.3–127.4) in the RM group. The fraction of the total P_{max} nBED accounted for by the SBRT P_{max} nBED for the RM patients ranged from 0.54 to 0.78 and that for the no-RM patients ranged from 0.04 to 0.53.

Conclusions: SBRT given at least 5 months after conventional palliative radiotherapy with a reirradiation thecal sac P_{max} nBED of 20–25 $Gy_{2/2}$ appears to be safe provided the total P_{max} nBED does not exceed approximately 70 $Gy_{2/2}$, and the SBRT thecal sac P_{max} nBED comprises no more than approximately 50% of the total nBED. © 2010 Elsevier Inc.

Radiation myelopathy, Stereotactic body radiotherapy, Radiosurgery, Biologically effective dose, re-irradiation.

- 5 mo or greater interval
- Cumulative Pmax to thecal sac=70Gy/2Gy equivalent (α/β=2 for cord)
- SBRT pmax comprises no more than 50% of total nBED

Principles of Spinal Re-RT

1. Keep cumulative BED Gy2 to ≤135.5

$$\text{BED Gy}_{(\alpha/\beta)} = n \times d\,[1 + d/(\alpha/\beta)]$$

where d = dose per fraction; n = number of fractions; *α/β = 2 for spinal cord*

2. No single course w/ BED ≥102Gy2

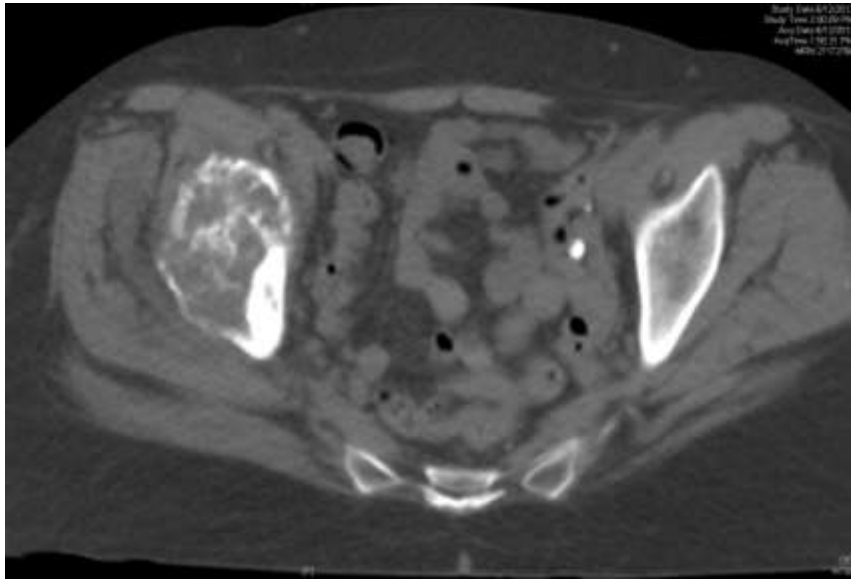
3. Re-RT interval ≥6 mos, if cord compromise imminent, can consider >2 mos

Scenario 2: MESCC Recommendation

- Dexamethasone 10mg x 1, 4mg q6hrs
- Discussed goals/hopes, wants to try “everything” to stay alive longer to be with family for holidays, does not want surgery
- SF RT 8G x 1 → chemotherapy
- Myelopathy risk low (based on Nieder et al. data ~3%)
- Remained ambulatory, died 5 months later (in hospice for 6 days)

Scenario 3: Good prognosis bone metastases

- 62 yo woman w/ hx of DCIS of R breast (2004, s/p BCT) progressive R hip pain (7/10) worse with weight-bearing (10/10), non-ambulatory
- Work-up: bone only met disease with 8 x 9cm right acetabular lesion, bx → met breast adenoca (+/+/-)
- Prognosis is >1 year
- No surgical option (lesion too extensive), plasty also not technically feasible
- How to optimize pain and disease control given good life expectancy?

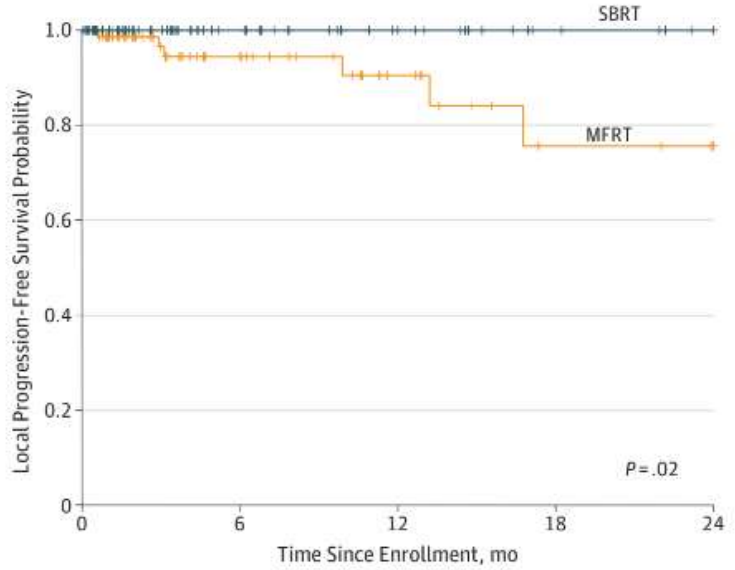


SBRT for Painful Non-spine Bone Metastases

Nguyen et al. *JAMA Oncology* 2019: Single institution, phase II RCT, non-inferiority study of 160 pts with painful bone mets randomized to SBRT (12-16Gy SF) vs. MFRT (30Gy in 10fx); Primary endpoint pain response

- Pain Response(CR+PR) SBRT>MFRT:
  - 2 weeks (62% vs. 36%, p=0.01)
  - 3 months (72% vs. 49%, p=0.03)
  - 9 months (77% vs. 46%, p=0.03)
- Local Control SBRT>MFRT
  - 1 year (100% vs. 90.5%, p=0.01)
  - 2 years (100% vs. 75.6%, p=0.01)

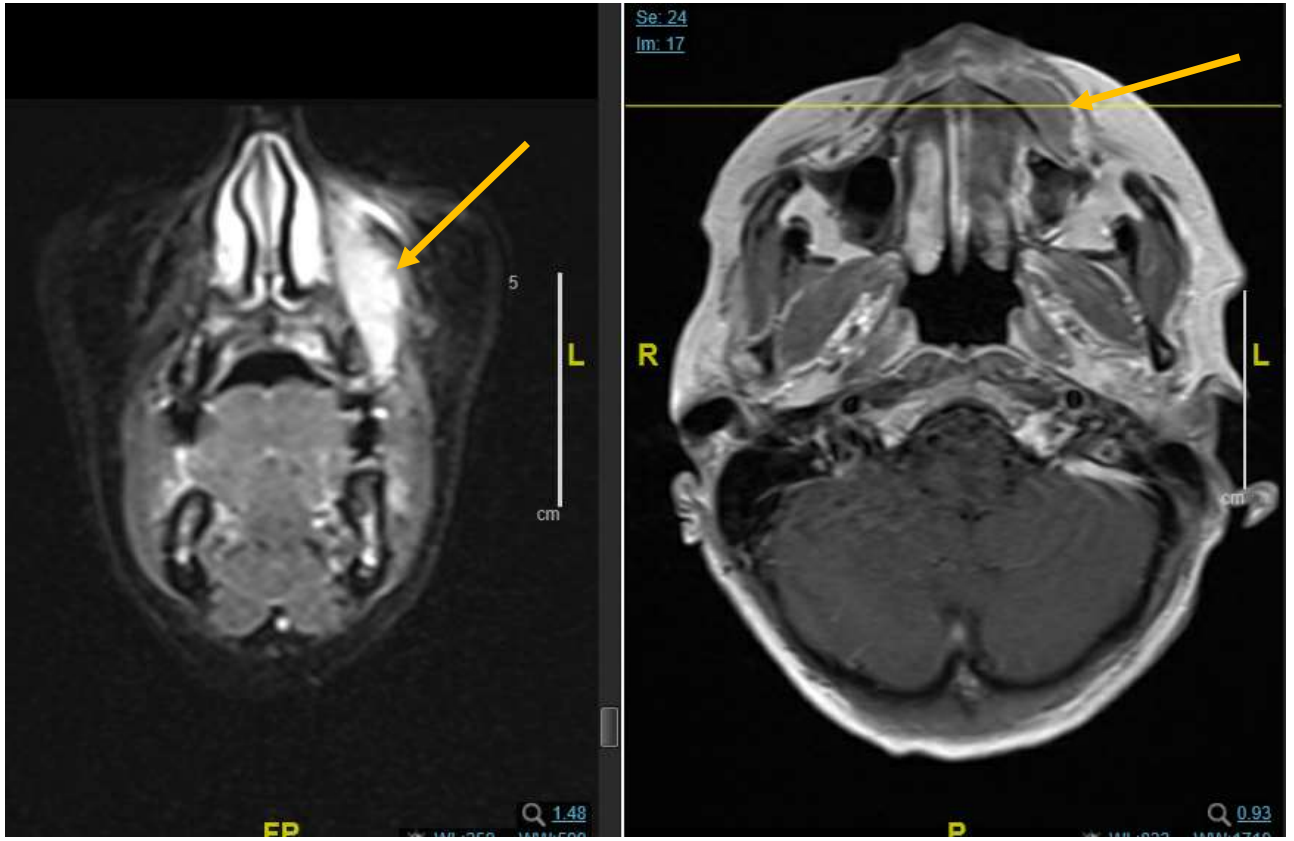
Figure 2. Local Progression-Free Survival According to Treatment



MFRT indicates standard-dose multifraction radiation therapy (10 fractions of 3 Gy each, for a total of 30 Gy); SBRT, high-dose, single-fraction stereotactic radiation therapy with a dose of 12 Gy or 16 Gy (solid line).

Recommendation and Clinical Scenario 4:

- SBRT on clinical trial (35Gy in 5 fractions)
- 3.5 years later develops painful swelling in L maxillary region, has lung, liver metastases, prognosis ~6 months



Head and Neck Palliation

International Journal of Radiation Oncology biology • physics
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Critical Review

Palliative Radiation Therapy for Head and Neck Cancers

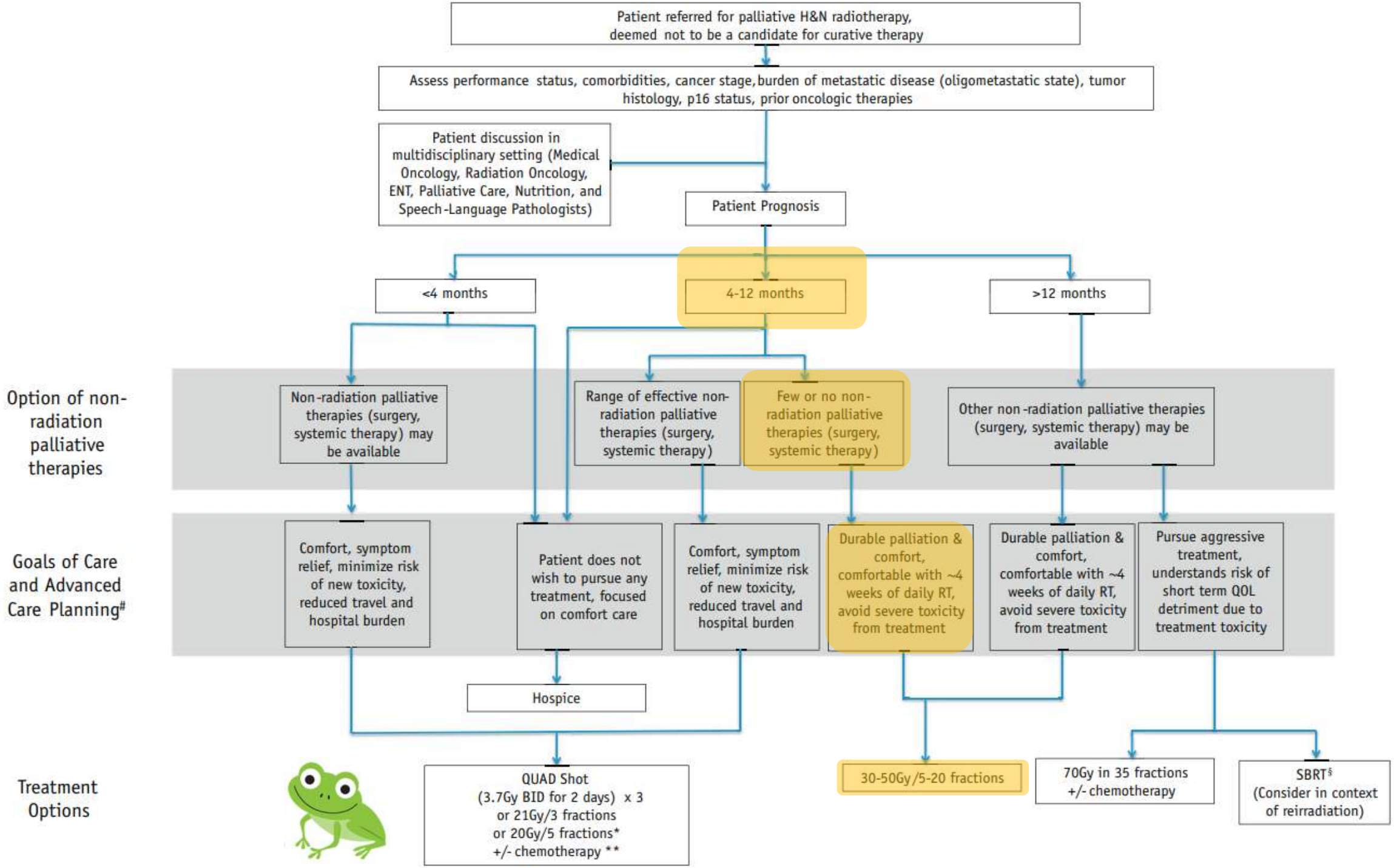
Amardeep S. Grewal, MD, Joshua Jones, MD, and Alexander Lin, MD

Varieties of regimens have been studied

- Short to intermediate course conventional regimens, eg: 4Gy x 5, Quad Shot (3.7Gy bid x 2 days repeated up to 3 cycles, q3-4 wk), 8Gy x 3, 3Gy x 10, 6Gy x 5, 2.4Gy x 16,
- SBRT regimens (eg, 35Gy in 5 fractions)
- Protracted higher dose (eg, 50-72Gy) regimens

Review is critical summary of data, with principles in RT palliative regimen selection being:

- Multi-D assessment
- Prognosis
- Consideration of other palliative therapies available and urgency of initiation
- Patient goals/values (larger goals and practical issues like travel, side effects)


Patient referred for palliative H&N radiotherapy, deemed not to be a candidate for curative therapy
Assess performance status, comorbidities, cancer stage, burden of metastatic disease (oligometastatic state), tumor histology, p16 status, prior oncologic therapies
Patient discussion in multidisciplinary setting (Medical Oncology, Radiation Oncology, ENT, Palliative Care, Nutrition, and Speech-Language Pathologists)
Patient Prognosis
<4 months
4-12 months
>12 months
Option of non-radiation palliative therapies
Non-radiation palliative therapies (surgery, systemic therapy) may be available
Range of effective non-radiation palliative therapies (surgery, systemic therapy)
Few or no non-radiation palliative therapies (surgery, systemic therapy)
Other non-radiation palliative therapies (surgery, systemic therapy) may be available
Goals of Care and Advanced Care Planning#
Comfort, symptom relief, minimize risk of new toxicity, reduced travel and hospital burden
Patient does not wish to pursue any treatment, focused on comfort care
Comfort, symptom relief, minimize risk of new toxicity, reduced travel and hospital burden
Durable palliation & comfort, comfortable with ~4 weeks of daily RT, avoid severe toxicity from treatment
Durable palliation & comfort, comfortable with ~4 weeks of daily RT, avoid severe toxicity from treatment
Pursue aggressive treatment, understands risk of short term QOL detriment due to treatment toxicity
Hospice
Treatment Options
QUAD Shot (3.7Gy BID for 2 days) x 3 or 21Gy/3 fractions or 20Gy/5 fractions* +/- chemotherapy **
30-50Gy/5-20 fractions
70Gy in 35 fractions +/- chemotherapy
SBRT§ (Consider in context of reirradiation)

Summary

1. Bone metastases, non-complicated: single fraction RT should be considered in all pts, with discussion benefits/risks (slightly higher need for retreatment).
2. Complicated due to bone instability: Mirels & SINS criteria key to determining fracture risk and need for stabilization. Complicated setting where bone remodeling is an issue, consider more dose intense regimens.
3. Complicated due to cord compression: Standard is decompression → RT for pts who qualify, but data support weighing nonsurgical management in light of prognosis, goals. Short course RT, eg, 4Gy x 5 and 8Gy x 1 are optimal in short life expectancies
4. Complicated due to prior RT: Keep to (a) cumulative BED (cord alpha/beta of 2) max 135-140Gy2, (b) at least 5-6 mo between courses, (c) no course with dose intensity ≥102Gy2
5. Good prognosis pts w/ painful bone metastases: Data suggest better local control (possibly pain outcomes) in pts receiving SBRT. Evolving area or research.
6. Head and neck palliation: Requires multi-disciplinary assess, consideration of prognosis, goals, other treatments available. 2019 IJROPB review provides helpful summary of RT regimens.