The Role of Radiotherapy for Bone Metastases

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www.rvh.on.ca

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Objectives

- To learn the difference between complicated and uncomplicated bone metastases (mets) and their treatment
- The role of RT in complicated and uncomplicated bone metastases
- The efficacy and side effects of RT for bone metastases
- Introduction to radiopharmaceuticals
- An overview of vertebroplasty/kyphoplasty

Conflicts of Interest

- I am a radiation oncologist
- I do not accept any outside funding except for food (Varian, Electa)

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Complicated Bone Metastases

- Impending or actual pathological fracture
- Spinal cord/cauda equina compression
- Significant soft tissue component extending beyond the bone which may be causing neuropathic/radicular pain
- Typically receive higher doses of fractionated RT (e.g. 20Gy/5F or 30Gy/10F)

Uncomplicated Bone Metastases

Everything else (e.g. rib met, humeral met)

Typically can receive a single fraction of 8Gy

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Indications

1. Bone pain
2. Impending or actual pathological fractures
   RT alone or post-operative
3. Neurological complications
   - Spinal cord compression
   - Nerve root compression
   - Base of skull metastases

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Response Rates

Based on 16 RCTs, a systematic review and the ASTRO bone mets guildelines:

No difference in response rates between 8Gy/1F and multi-fraction regimens (e.g. 20Gy/5F)

~60 – 70% overall response rate

~25 – 30% complete response rate

Median time to pain relief is 2 - 3 weeks

Chow E, et al. Clin Oncol (R Coll Radiol). 2012 Mar;24(2):112-24.

Lutz ST, et al. Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 4, pp. 965–976, 2011

Response Rates

Median duration of pain relief is 3 – 6 months

Response by site (and perhaps duration of response): breast > prostate > lung

Retreatment rates are 20% for single fraction treatments and 8% for multi-fraction treatments

Physicians may be more willing to retreat patients who have received only a single fraction

Response Rates

There is no evidence that a single 8 Gy fraction provides inferior pain relief to a more prolonged course of treatment in spinal mets

A subset analysis from RTOG 97-14 showed no difference in pain relief in spine sites compared to extremity sites and no difference in response between cervical spine, thoracic spine or lumbar spine sites

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Neuropathic Pain

- TROG 96.05 compared 8Gy/1F and 20Gy/5F in 272 patients with neuropathic pain from bone metastases.
- The overall response rates for 8Gy/1F and 20Gy/5F were 53% and 61%, respectively ($P = 0.18$), with complete response rates of 26% and 27%, respectively ($P = 0.89$).
- The estimated median time to treatment failure (TTF) was 2.4 months and 3.7 months for 8Gy/1F and 20Gy/5F, respectively

Neuropathic Pain

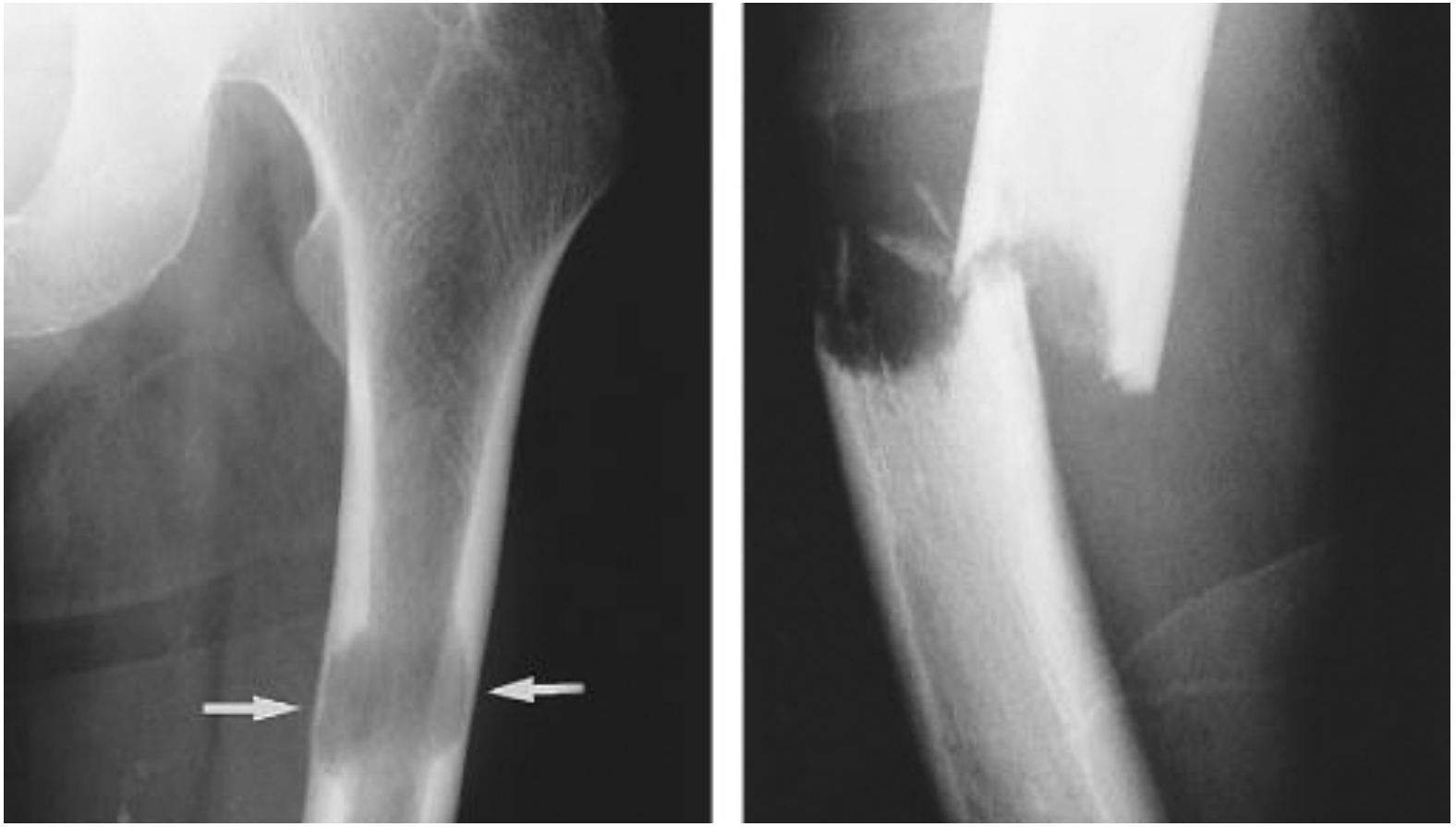
There was a trend for shorter time to treatment failure in the single fraction arm with a hazard ratio of 1.35 (P = 0.056).

There were no significant differences in the rates of re-treatment, spinal cord compression or pathological fracture between the two arms.

Therefore, there is weak evidence for using a higher dose/fractionation for bone mets causing neuropathic pain

Impending Pathological Fracture

- Cortical lytic lesions > 2.5 cm in the femur, esp. in the femoral neck, intertrochanteric region or the subtrochanteric region



Impending Pathological Fracture

Increasing pain with weight bearing over time

> 50% circumferential cortical destruction of the femur

Persistent pain or radiographic progression in the femur after radiation

These patients should see an orthopedic surgeon urgently for consideration of prophylactic surgical fixation

Mirel's Score

Mirels' scoring system

Score	Site of lesion	Size of lesion	Nature of lesion	Pain
1	Upper limb	< 1/3 of cortex	Blastic	Mild
2	Lower limb	1/3–2/3 of cortex	Mixed	Moderate
3	Trochanteric region	> 2/3 of cortex	Lytic	Functional

(Adapted and published with permission of Lippincott Williams & Wilkins from Mirels H. Metastatic disease in long bones: a proposed scoring system for diagnosing impending pathologic fractures. *Clin Orthop Relat Res*. 1989;249:256–264.)

Clin Orthop Relat Res. 2010 Oct; 468(10): 2825–2827.

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Mirel's Score

Mirels' score	Clinical recommendation
≤ 7 (4% fracture risk)	Radiotherapy and observation
8 (15%)	Use clinical judgment
≥ 9 (9=33%;10=72%)	Prophylactic fixation

Clin Orthop Relat Res. 2010 Oct; 468(10): 2825–2827.

Post-operative RT

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ROLE OF POSTOPERATIVE RADIATION THERAPY AFTER STABILIZATION OF FRACTURES CAUSED BY METASTATIC DISEASE

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Purpose: Although orthopedic stabilization is frequently performed for pathological fractures caused by metastatic disease, no data is available to support the value of postoperative radiation therapy (S+RT) in this setting.
Methods and Materials: We reviewed 64 orthopedic stabilization procedures in 60 consecutive patients with metastatic disease to previously unirradiated weight-bearing bones with pathological or impending pathological fracture (femur 91%). Thirty-five sites that received adjuvant S+RT were compared to 29 sites that were treated with surgery alone (SA). Many potential prognostic variables were evaluated. Endpoints were: functional status (FS) of the extremity (1 = normal pain free use; 2 = normal use with pain, 3 = significantly limited use; 4 = nonfunctional extremity), subsequent orthopedic procedures to the same site, and survival following surgery.
Results: At the univariate level, S+RT ($p = 0.02$) and prefracture FS ($p = 0.04$) were the only significant predictors of patients achieving an FS of 1 or 2 after surgery. On multivariate analysis, only postoperative RT was significantly ($p = 0.02$) associated with attaining FS of 1 or 2 after surgery. The predicted probability of achieving FS 1 or 2 at any time was 53% for S+RT vs. 11.5% or SA (multiple logistic regression, $p < 0.01$). Evaluation of FS following surgery revealed that S+RT group had significantly better function in the 1–3, 3–6, and 6–12 month postoperative

Int. J. Radiation Oncology Biol. Phys., Vol. 31, No. 1, pp. 43-49, 1995

Post-operative RT

64 stabilization procedures in 60 consecutive patients with pathological or an impending pathological fracture (femur 91%).

35 sites that received adjuvant radiation (S+RT) were compared to 29 sites that were treated with surgery alone (SA).

RT started within 6 weeks (mean = 2 weeks)

Median dose of RT = 30Gy/10F

Endpoints were: functional status (FS) of the extremity (1 = normal pain free use; 2 = normal use with pain, 3 = significantly limited use; 4 = nonfunctional extremity), subsequent orthopedic procedures to the same site, and survival.

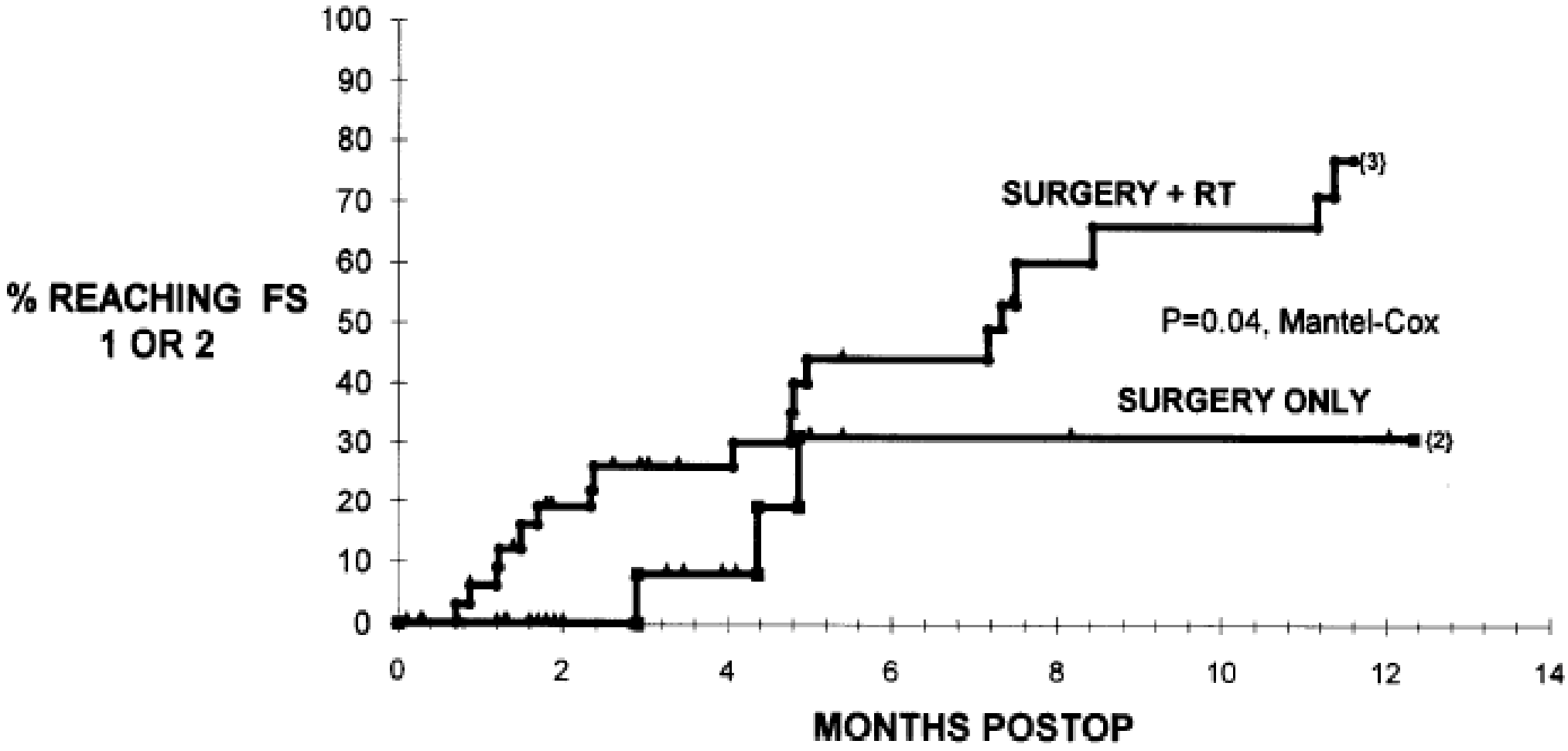
Post-operative RT

Table 1. Patient, tumor and fracture characteristics

	Surgery only	Surgery + RT
Number of procedures	29	35
Number of patients	[illegible]	[illegible]
Age at diagnosis of primary	Mean 65 Y.O.	Mean 58 Y.O.
	[illegible]	[illegible]
Gender	55% Female	69% Female
	45% Male	31% Male
Primary site:	38% Breast	29% Breast
	21% Prostate	6% Prostate
	14% Lung	31% Lung
	3% Unknown	11% Unknown
	3% Renal	9% Renal
	20% Other	14% Other
Type of fracture	72% Pathological	51% Pathological
	28% Impending Pathological	49% Impending Pathological
Fracture site	89% Femur	91% Femur
	4% Humerus	6% Humerus
	7% Other	3% Other
Extremity functional status before fracture	Mean Score: 1.62	Mean Score: 1.17

Breast + Prostate = 59% (SA) vs. 35% (S+RT)

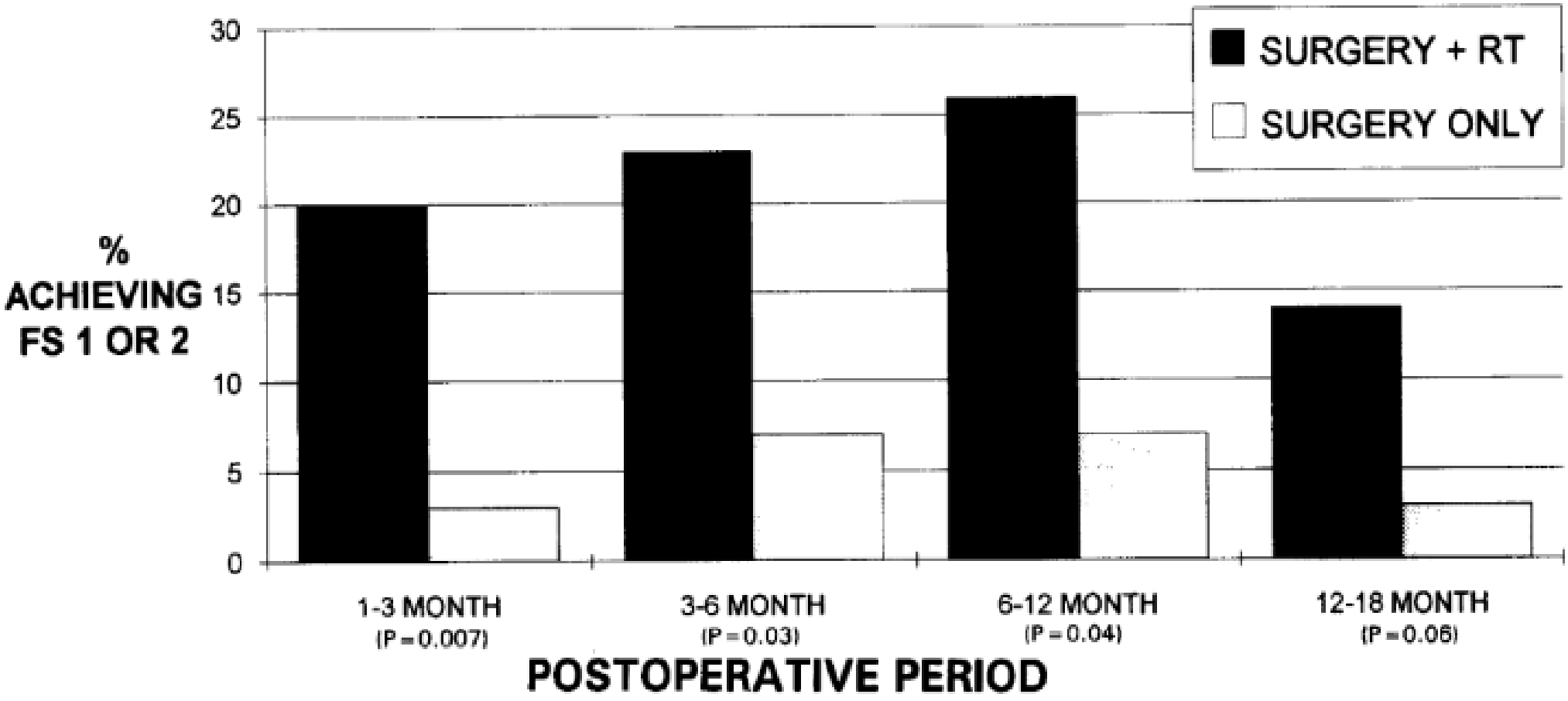
Post-operative RT



Post-operative RT

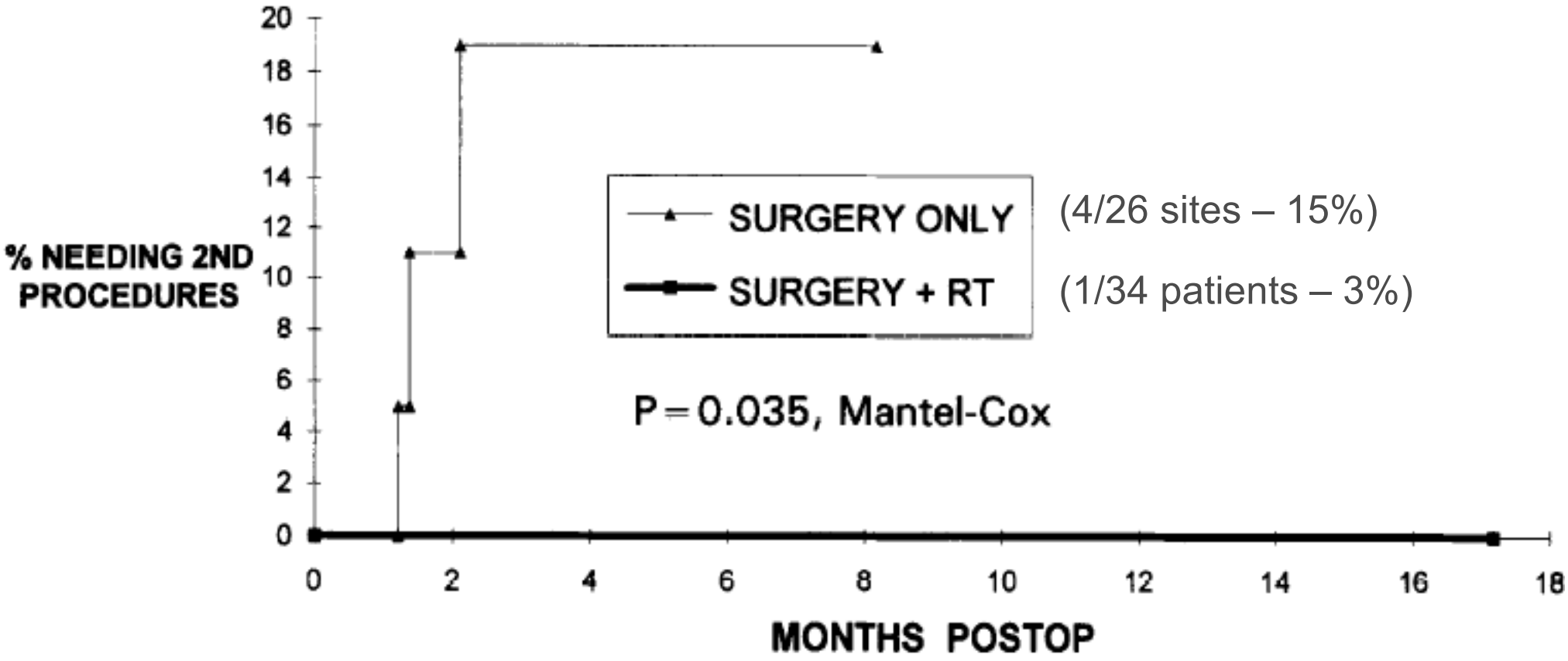
- On univariate analysis, S+RT ($p = 0.02$) and prefracture FS ($p = 0.04$) were the only significant predictors of patients achieving an FS of 1 or 2 after surgery.
- On multivariate analysis, only postoperative RT was significantly ($p = 0.02$) associated with attaining FS of 1 or 2 after surgery.
- The predicted probability of achieving FS 1 or 2 at any time was 53% for S+RT vs. 11.5% or SA (multiple logistic regression, $p < 0.01$).

Post-operative RT



The S+RT group had significantly better functional status in the 1-3, 3-6, and 6-12 month postoperative periods.

Post-operative RT



Second orthopedic procedures to the same site due to pain associated with loosening of the prosthesis were more common in the SA group than the S+RT group (log rank, p = 0.03).

Post-operative RT

Median survival: 3.3 months (SA) vs. 12.4 months (S+RT) (log rank, p = 0.02)

On Cox multivariate analysis of survival, only postoperative radiation therapy was significantly associated with improved survival (p = 0.025).

Improved survival may be due to:

1. More favorable patients being referred for RT (section bias) or
2. Improved functional status in the S+RT group.

Post-Operative RT

- The optimal dosing of post-operative RT is not known
- However, longer schedules, like 30Gy/10F, are most commonly used since the intent is to treat microscopic/macroscopic residual disease
- 20Gy/5F is also acceptable

Treatment Planning (ASTRO Guidelines)

- Treatments to the spinal bones should be prescribed to the mid-vertebral body, with inclusion of at least one vertebral body above and below the painful vertebral body level or levels.
- Other sites should be prescribed as an applied dose for single fields and a mid-plane dose for POP

RT Side Effects

Dependent on where the met is located

Radiation dermatitis

Mild fatigue

Nausea if treating in the region of the upper abdomen (liver and stomach)

- granisetron 1 mg 1 hour prior to RT or ondansetron 1 hr prior to and 8 hr after RT

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RT Side Effects

- Dysphagia/odynophagia if treating in the region of the esophagus
- Sore throat (C-spine, upper T-spine)
- Dry cough (trachea)

RT Side Effects

~33% chance of a pain flare

Maybe a higher chance with single fraction

Usually starts within 5 - 10 days of starting RT

Lasts 1 – 3 days

Dexamethasone helps prevent pain flares

- Mild impairment of healing post-op
- Can raise blood sugars
- Insomnia/anxiety

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Dexamethasone Pain Flares – SC.23

298 patients received either 8 mg of dexamethasone or placebo at least 1 h before starting RT

RT consisted of 8Gy/1F

Dexamethasone was continued for 4 more days post-RT (total of 5 days)

Patients reported their worst pain scores and opioid analgesic intake before treatment and daily for 10 days after RT

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Dexamethasone Pain Flares – SC.23

Pain flare was defined as at least a two-point increase on a scale of 0–10 in the worst pain score with no decrease in analgesic intake, or a 25% or greater increase in analgesic intake with no decrease in the worst pain score from days 0–10, followed by a return to baseline levels or below.

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Dexamethasone Pain Flares – SC.23

- 26% of the dexamethasone group and 35% of the placebo group had a pain flare (difference of 8.9%, one-sided p=0·05).
- Two grade 3 and one grade 4 hyperglycaemic events occurred in the dexamethasone group (without known clinical effects) compared with none in the placebo group.

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Retreatment

- Suitable for those with an initial response, minimal response, or no response
- Hayashi reported a 50% response rate to repeat RT (Radiat Med. 2002 Sep-Oct;20(5):231-6).
- 100% RR for those with an initial CR and 41% for those with an initial PR
- Median duration of pain relief = 5 months.

Retreatment

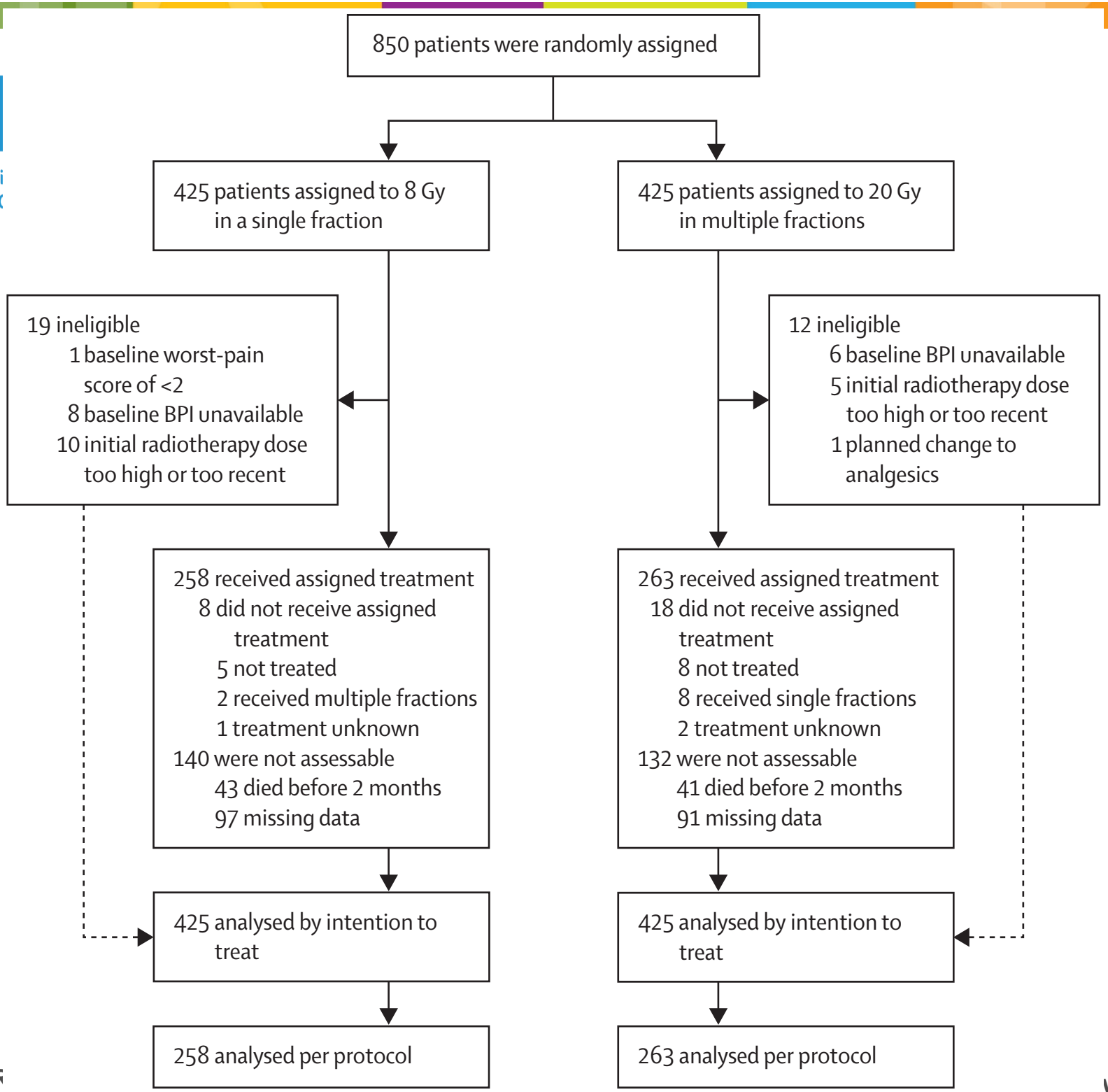
- Mithal reported similar RR to a 2nd and 3rd course of RT as to the initial course – 85% (Int J Rad Onc Bio Phys 1994)
- Jeremic found a RR of 74% for patients with an initial pain response (n = 109) and a RR of 46% in those with no initial response (n = 26) in a prospective study (Radiother Oncol 1999)

Retreatment - RCT

Chow E, et al. Lancet Oncol. 2014 Feb;15(2):164-71.

850 patients previously treated for bone mets with RT were randomly assigned to receive either 8Gy/1F or 20Gy/5F (20Gy/8F if treating over the spine or whole pelvis if the previous RT was given in multiple fractions)

The primary endpoint was overall pain response (complete + partial) at 2 months



Retreatment - RCT

- In the intention-to-treat analysis, 118 (28%) patients allocated to 8 Gy and 135 (32%) allocated to 20 Gy had an overall pain response (p = 0·21)
- In the per-protocol analysis, 116 (45%) of 258 patients and 134 (51%) of 263 patients, respectively, had an overall pain response to treatment (p = 0·17)
- Freedom from pain progression was similar between groups

Retreatment - RCT

Patients receiving 20Gy had less fatigue

However, 14 days after receiving therapy, patients receiving 20Gy had more frequent and increased lack of appetite (66% *vs* 56%; p=0·011), vomiting (23% *vs* 13%; p=0·0010), diarrhoea (31% *vs* 23%; p=0·018), and skin reddening (24% *vs* 14%; p=0·0020).

Retreatment - RCT

Overall response rates were similar whether or not patients had a response to the initial RT or not and whether they had a single or multiple fractions with the 1st course of RT (all ~45 – 50% response rates)

Conclusions: In patients requiring repeat radiation therapy, treatment with 8Gy/1F seems to be non-inferior and less toxic than 20Gy/5F or 20Gy/8F

Spinal Retreatment

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ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 5, pp. 1446–1449, 2006

0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2006.07.1383

CLINICAL INVESTIGATION **Normal Tissue**

UPDATE OF HUMAN SPINAL CORD REIRRADIATION TOLERANCE BASED ON ADDITIONAL DATA FROM 38 PATIENTS

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Purpose: To update a combined analysis of all published clinical data.
Methods and Materials: We collected data from 38 additional patients treated in our department or published in four different reports and calculated the biologically effective dose (BED) according to the linear-quadratic

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Spinal Retreatment

- Small risk of myelitis if total BED is ≤135.5 Gy2, interval is ≥6 months between courses and the dose of each course is ≤98 Gy2
- No case of myelitis has been reported if the total BED is 120 Gy2, interval is ≥6 months and the dose per course is ≤98 Gy2
- Cases of myelitis usually don't occur ≤6 months (most likely ≥12 months)

Radiopharmaceuticals

- ^{89}Sr and ^{152}Sm are bone seeking radioisotopes that emit radiation (electrons and gamma rays, respectively)
- Radiopharmaceuticals are taken up most actively in areas of bone growth present in osteoblastic metastases
- They have been used historically to treat more widespread osteoblastic metastases

Radiopharmaceuticals

- Low incidence of mild - moderate hematosuppression (Pl and WBC)
- Patients at highest risk for myelosuppression have widespread bone marrow involvement and significant prior myelosuppressive therapy, e.g. chemotherapy
- Nadir in blood counts 6-7 weeks after treatment and recovery by 8-12 weeks
- Pain flare occur in 10-40% of patients

Radiopharmaceuticals

Strontium-89 and samarium-153 have a similar time until pain relief, overall efficacy, and risk of toxicity

Pain relief starts at 2 - 3 weeks post treatment

Partial response rates of 55-95%

Complete response rates of 5-20%

A mean duration of pain relief of 3-6 months

Radiopharmaceuticals

Radium-223 (^{223}Ra) is an alpha emitting radionuclide

As a calcium mimetic, radium-223 is bone seeking and preferentially binds to newly formed bone matrix, targeting osteoblastic mets

Alpha particles have a high linear energy transfer (i.e. cause intense RT damage) with a very short range in tissue of < 100 µm (10 – 20 cell diameters)

Radium-223

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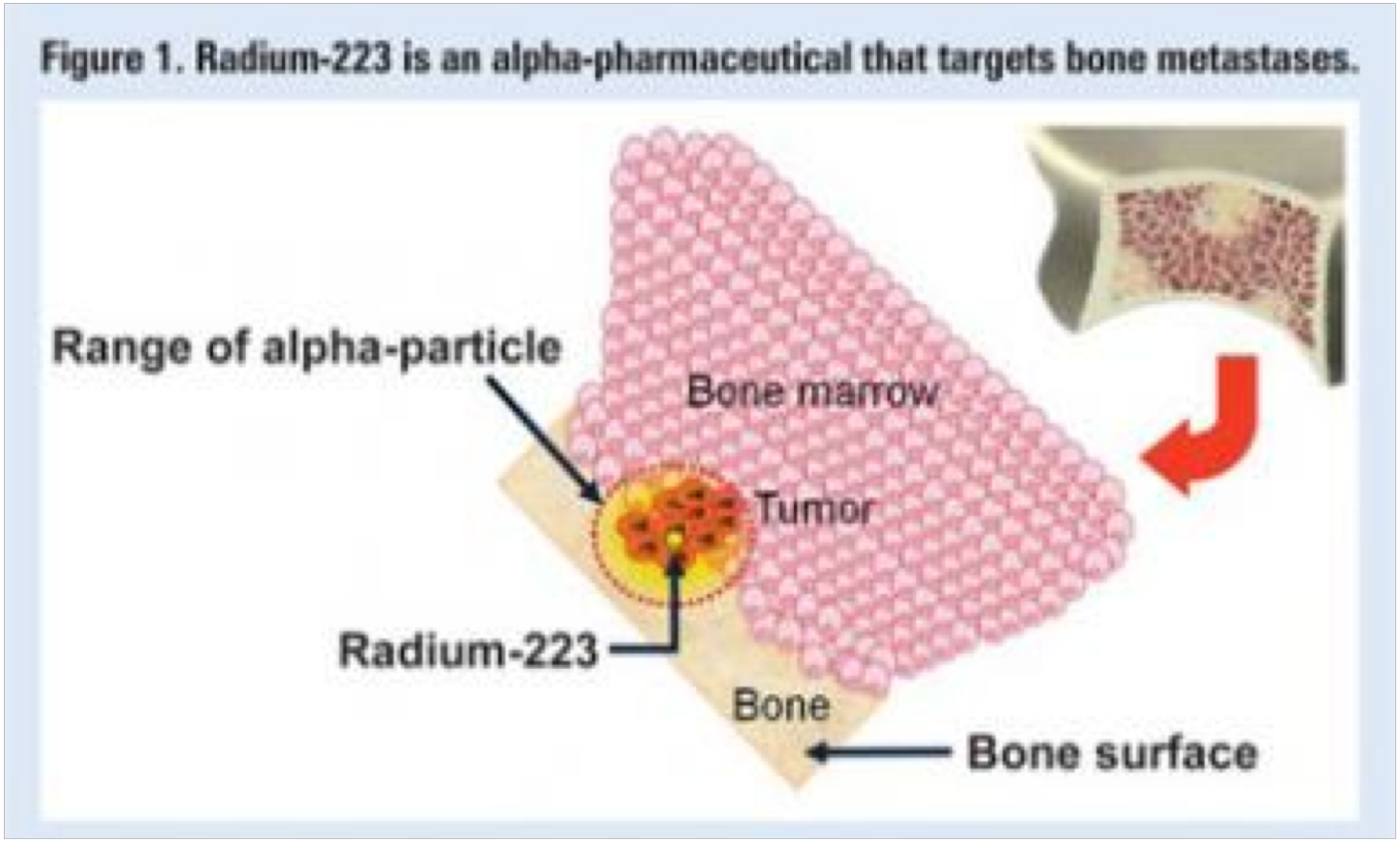

^{223}Ra is thought to have increased anti-tumour effects with less bone marrow damage

http://gucasym.asco.org/radium-223-crpc-bone-metastases-improving-survival-and-delaying-skeletal-related-events

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Radium 223 ALSYMPCA

Parker C, et al. N Engl J Med 2013; 369: 213-23

Sartor O, et at. *Lancet Oncol* 2014; 15: 738–46

RCT (n = 921) comparing Ra-223 vs placebo in patients with symptomatic castration-resistant prostate cancer with ≥ 2 bone metastases and no visceral metastases

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Radium-223 ALSYMPCA

- Patients had previously either received or were unsuitable for docetaxel
- 6 injections of Ra-223 q4 weeks or placebo

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Radium-223 ALSYMPCA

Ra-223 significantly improved:

- Overall survival (14.0 vs. 11.2 months; p = 0.00185)
- Median time to first SRE (15.6 mo vs 9.8 mo, p = 0.00037)

There was minimal myelosuppression:

Gr 3/4 neutropenia in 2.2% and gr 3/4 thrombocytopenia in 6.3% of Ra-223 patients

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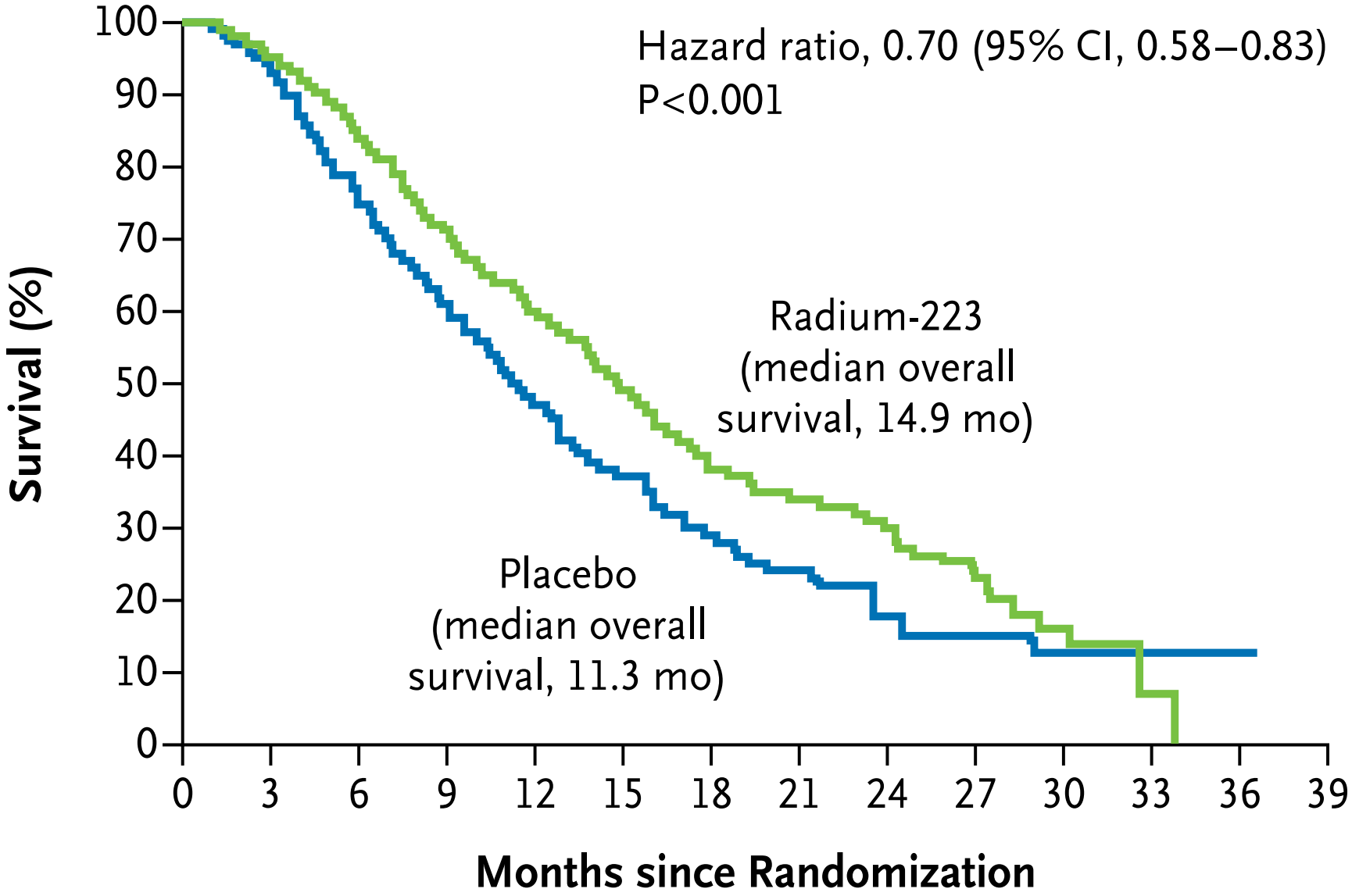
ALSYMPCA

Overall Survival



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ALSYMPCA
Skeletal Related Events

- Defined as the use of RT, a symptomatic pathological fracture, a SCC, or a tumour-related surgical intervention
- Time to first symptomatic skeletal event was longer with radium-223 than with placebo (median 15·6 months *vs* 9·8 months; hazard ratio = 0·66, p=0·00037).

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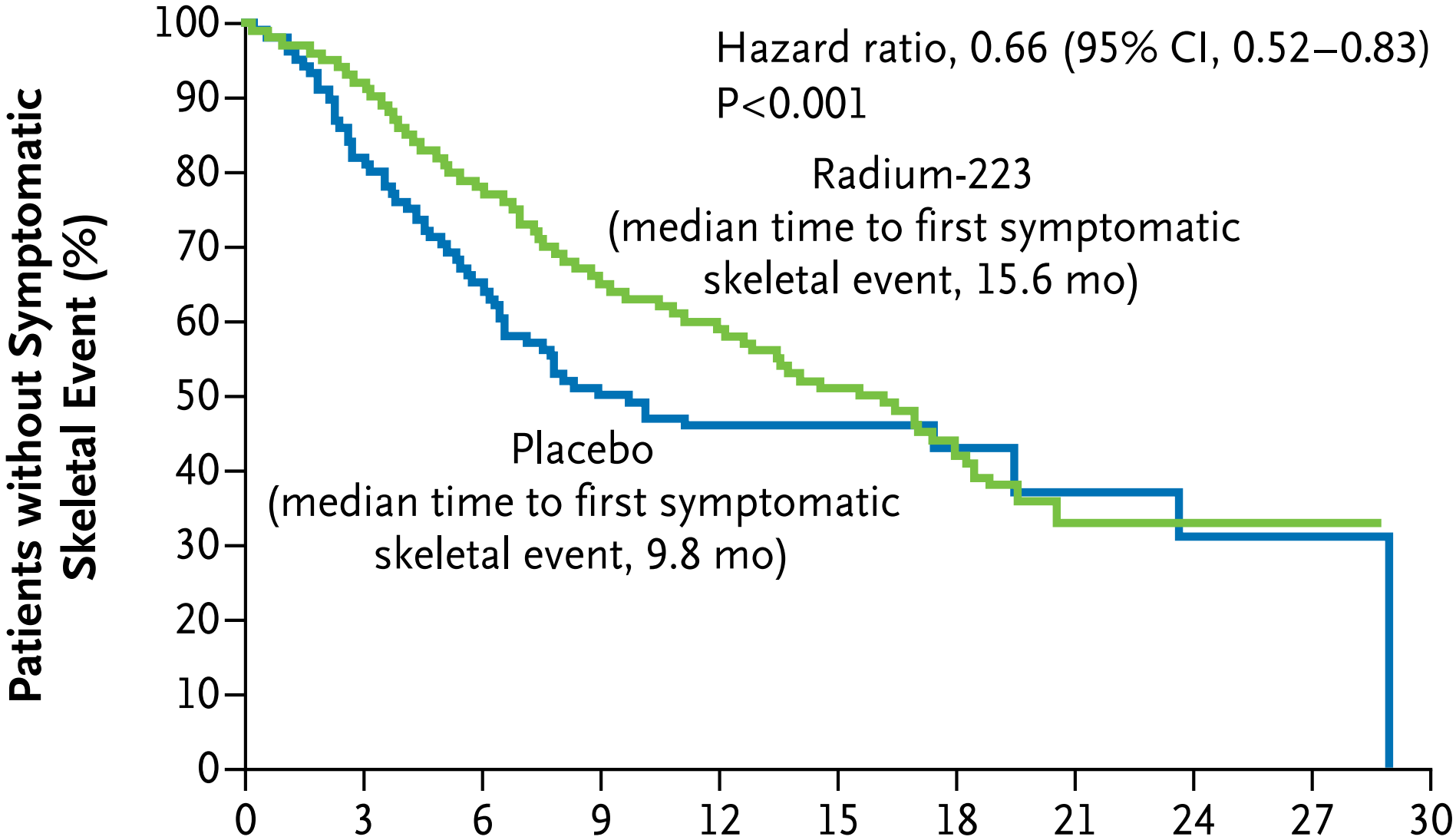
ALSYMPCA
Skeletal Related Events



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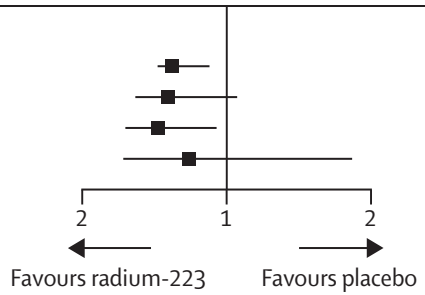
ALSYMPCA
Skeletal Related Events

	Radium-223 (n=614)		Placebo (n=307)		HR (95% CI)	p value*
	Number of patients (%)	Median time to first event, months (95% CI)	Number of patients (%)	Median time to first event, months (95% CI)		
Individual symptomatic skeletal event components						
External beam radiotherapy	186 (30%)	17·1 (14·1–19·8)	105 (34%)	17·5 (7·9–29·0)	0·67 (0·53–0·85)	0·00117
Symptomatic pathological bone fracture	32 (5%)	NE	20 (7%)	NE	0·62 (0·35–1·09)	0·10
Spinal cord compression	25 (4%)	NE	21 (7%)	NE	0·52 (0·29–0·93)	0·03
Tumour-related orthopaedic surgical intervention	12 (2%)	NE	7 (2%)	NE	0·72 (0·28–1·82)	0·48



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Vertebroplasty

- RT can't eliminate mechanical pain from a pathological fracture
- Vertebroplasty involves percutaneous injection of polymethylmethacrylate (bone cement) into a fractured vertebral body
- Goals are to relieve pain and stabilize the pathologic fractures
- Most commonly used for osteolytic lesions

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Vertebroplasty

Side effects may include extravasation of cement outside of the vertebral bone, a traumatic fracture, pneumothorax, pulmonary embolism, fat emboli, dural tears, and death.

Osteoporosis (~80%), tumours (~15 – 20%) and hemangiomas (~2%)

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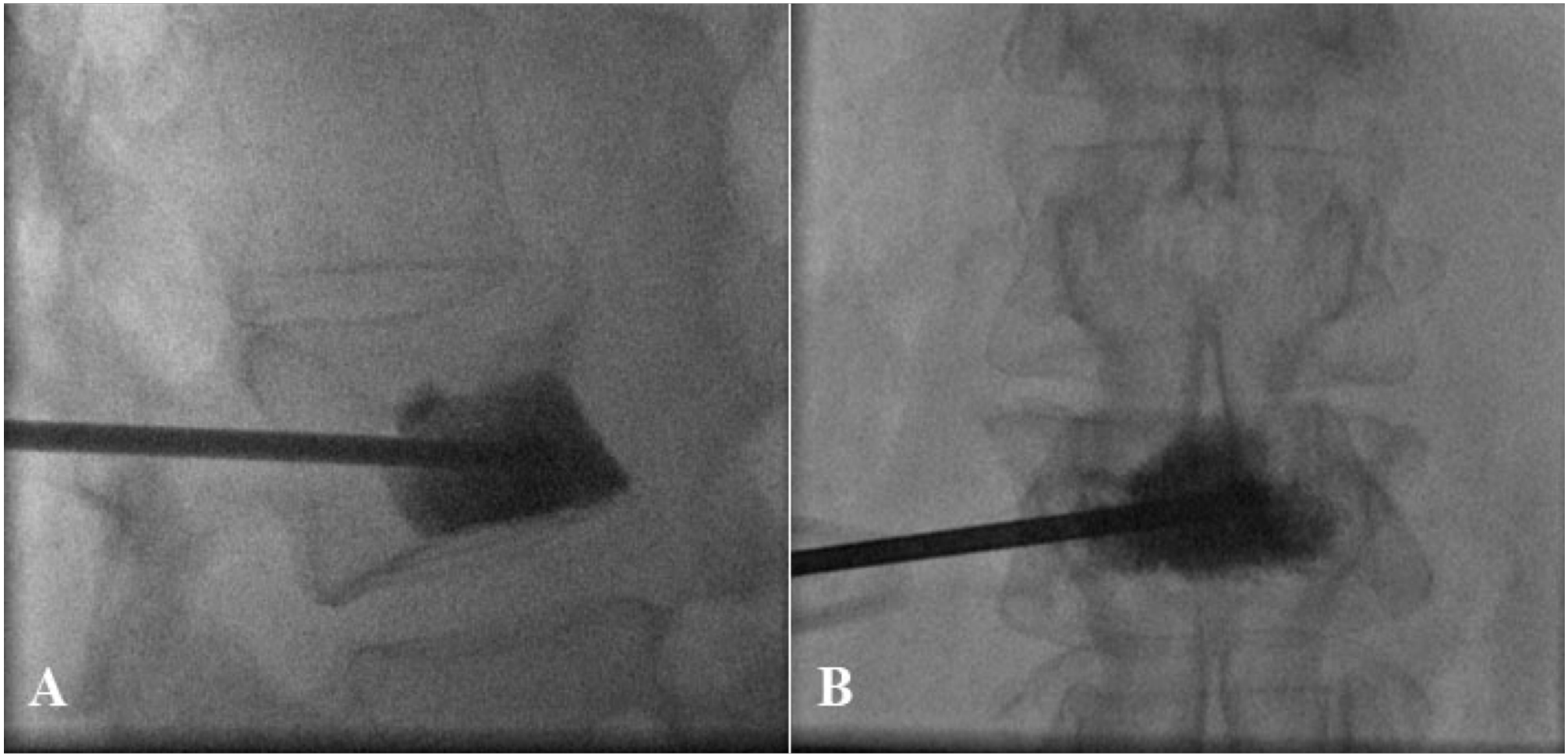
Vertebroplasty



http://www.joelgarrismd.com/vcftreatmentplasty.html

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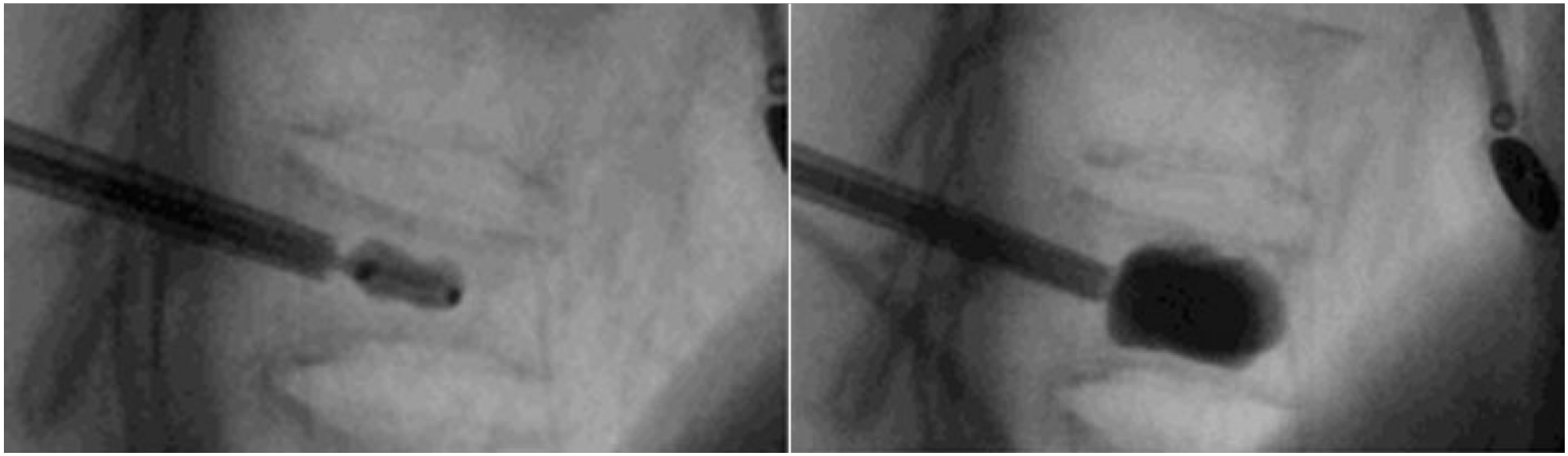
Kyphoplasty

Kyphoplasty involves inflating a balloon in the collapsed vertebra to restore its height before injecting the bone cement into this created space



http://www.joelgarrismd.com/vcftreatmentplasty.html

Kyphoplasty

Kyphoplasty may have a greater increase in vertebral body height and lower risk of cement extravasation vs. vertebroplasty

But kyphoplasty requires a general anesthetic, is much more costly and both a lengthier procedure time and period of monitoring after the procedure

Effectiveness

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The NEW ENGLAND JOURNAL of MEDICINE

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A Randomized Trial of Vertebroplasty for Painful Osteoporotic Vertebral Fractures

Rachelle Buchbinder, Ph.D., Richard H. Osborne, Ph.D., Peter R. Ebeling, M.D., John D. Wark, Ph.D., Peter Mitchell, M.Med., Chris Wriedt, M.B., B.S., Stephen Graves, D. Phil., Margaret P. Staples, Ph.D., and Bridie Murphy, B.Sc.

ORIGINAL ARTICLE

A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures

David F. Kallmes, M.D., Bryan A. Comstock, M.S., Patrick J. Heagerty, Ph.D., Judith A. Turner, Ph.D., David J. Wilson, F.R.C.R., Terry H. Diamond, F.R.A.C.P., Richard Edwards, F.R.C.R., Leigh A. Gray, M.S., Lydia Stout, B.S., Sara Owen, M.Sc., William Hollingworth, Ph.D., Basavaraj Ghdoke, M.D., Deborah J. Annesley-Williams, F.R.C.R., Stuart H. Ralston, F.R.C.P., and Jeffrey G. Jarvik, M.D., M.P.H.

Effectiveness

- Vertebroplasty vs. sham procedure for benign osteoporotic fractures
- No significant difference in disability and pain improvement (Kallmes et al), and pain improvement, physical functioning, quality of life, and perceived improvement (Buchbinder et al) between the two groups
- Current role of vertebroplasty?

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Summary

RT is an effective therapeutic option for symptomatic bone metastases with minimal side effects

RT can be used in conjunction with surgery and systemic therapies for the optimal management of bone metastases

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Questions?

Thank you for your time.