Associazione Italiana Radioterapia Oncologica

EFFICACIA DELLA CRIOTERAPIA IN ASSOCIAZIONE ALLA RADIOTERAPIA NEL TRATTAMENTO DEL DOLORE DA METASTASI OSSEE: UNO STUDIO DI FATTIBILITÀ TRAMITE ANALISI DELLA PROPENSITÀ

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Clinical Importance and Prognosis of Bone Metastases

	Disease prevalence, U.S. (in thousands)	Bone mets. incidence (%)	Median survival (mo)
Myeloma	75 - 100	70 - 95	24
Renal	198	20 - 25	12
Melanoma	467	14 - 45	6
Bladder	582	40	6 - 9
Thyroid	207	60	48
Lung	386	30 - 40	7
Breast	1,993	65 - 75	24
Prostate	984	65 - 75	36

NCI, 1997; International Myeloma Foundation, 2001.

Treatment Options

- Goals:
  - Attack the cancer
  - Strengthen the bone
  - Reduce symptoms

- Includes:
  - Systemic therapy
  - Local therapy

Local Therapies

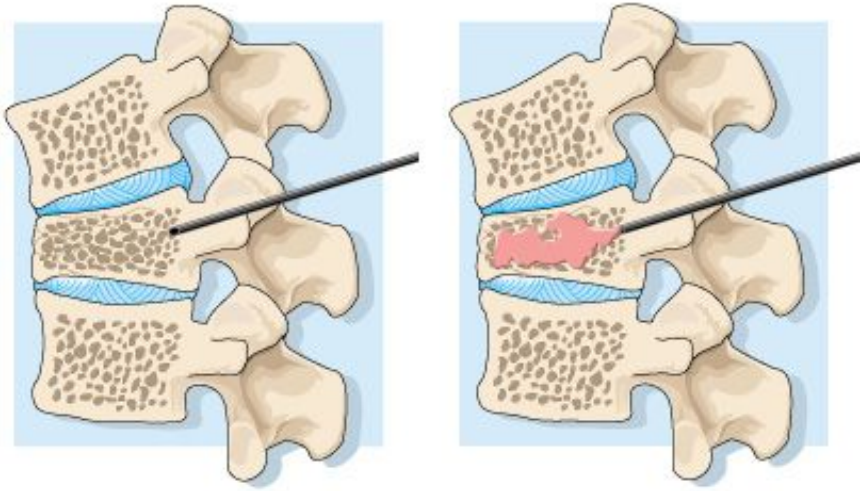
- Local therapies treat a limited number of locations; do not treat the whole body

- Types:
  - Radiotherapy
  - Interventional Radiology
  - Surgery

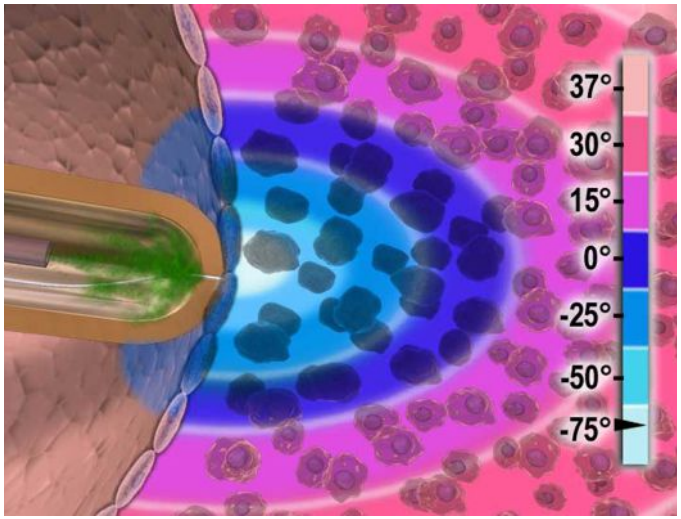
- Goals:
  - Relieve pain
  - Prevent fracture
  - Enhance mobility and function
  - Preserve quality of life

Interventional Radiology: Techniques

- Vertebroplasty:
  - Injection of bone cement to support weakened bones
  - Provides immediate and substantial pain relief



- Radiofrequency Ablation (RFA) and cryoablation
  - Minimally invasive procedures to “burn” or “freeze” a tumor
  - Desensitizes by killing nerve endings near the metastasis



Consensus on Palliative Radiotherapy Endpoint in Bone Metastases

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 5, pp. 1730–1737, 2012

0360-3016/$ - see front matter

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CLINICAL INVESTIGATION **Metastases**

UPDATE OF THE INTERNATIONAL CONSENSUS ON PALLIATIVE RADIOTHERAPY ENDPOINTS FOR FUTURE CLINICAL TRIALS IN BONE METASTASES

EDWARD CHOW, M.B.B.S.,* PETER HOSKIN, M.D.,† GUNITA MITERA, PH.D.(C),* LIANG ZENG, B.SC.(C),* STEPHEN LUTZ, M.D.,‡ DANIEL ROOS, M.D.,§ CAROL HAHN, M.D.,¶ YVETTE VAN DER LINDEN, M.D.,‖ WILLIAM HARTSELL, M.D.,# AND ESHWAR KUMAR, M.B.B.S. ** ON BEHALF OF THE INTERNATIONAL BONE METASTASES CONSENSUS WORKING PARTY

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Purpose: To update the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases by surveying international experts regarding previous uncertainties within the 2002 consensus, changes that may be necessary based on practice pattern changes and research findings since that time.

Methods and Materials: A two-phase survey was used to determine revisions and new additions to the 2002 consensus. A total of 49 experts from the American Society for Radiation Oncology, the European Society for Therapeutic Radiology and Oncology, the Faculty of Radiation Oncology of the Royal Australian and New Zealand College of Radiologists, and the Canadian Association of Radiation Oncology who are directly involved in the care of patients with bone metastases participated in this survey.

Results: Consensus was established in areas involving response definitions, eligibility criteria for future trials, re-irradiation, changes in systemic therapy, radiation techniques, parameters at follow-up, and timing of assessments.

Conclusion: An outline for trials in bone metastases was updated based on survey and consensus. Investigators leading trials in bone metastases are encouraged to adopt the revised guideline to promote consistent reporting. Areas for future research were identified. It is intended for the consensus to be re-examined in the future on a regular basis. © 2012 Elsevier Inc.

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Table 2. Updated consensus guideline

	Updated consensus guideline
Pain and Analgesic Assessment	Assessment of pain should be on a scale of 0 to 10, with boundaries of 0 representing no pain and 10 representing maximal pain
	Options for patient follow-up should include clinic visits, mailed questionnaires, telephone interviews, and/or electronic tallying, wherever available
	Incorporation of validated quality-of-life instruments specific to bone metastases, such as the EORTC QLQ-BM22 or EORTC QLQ-C15-PAL, is recommended for all clinical trials
	In addition to patient-based pain scoring, whether in person or remotely, assistance from caregivers, family members, or healthcare providers should be allowed if necessary
	Pain should be assessed by only the worst pain score for the previous 3 days
	Net pain relief may be considered in addition to evaluating absolute decreases in pain scores and changes in medication dosing
Response Guideline	Reirradiation of painful bone metastases should only be considered 4 weeks after completion of the initial treatment course
	A response category termed "indeterminate response" is recommended, representing response other than complete or partial response and pain progression

Table 2. Updated consensus guideline

	Updated consensus guideline
Clinical Trial Eligibility Criterion	An inclusion criterion requiring patients to report a worst pain score of at least 5 on a scale of 0 to 10, with 10 being the worst possible pain, may be recommended
	A "run-in" period, an interval of up to 1 week between analgesic dosing adjustment and initiation of irradiation, is recommended
	Changes in systemic chemotherapy, hormonal therapy or the use of bisphosphonates for 4 weeks before and after the delivery of radiotherapy are allowed, but recording and accounting for this in the statistical analysis is required
Radiation Techniques	For non-spine sites, radiation should be prescribed to an isodose for single incident fields and mid-plane for opposed fields
	Treatment using orthovoltage energies should be excluded from clinical trials
	Consensus participants were divided between prescribing to the mid-vertebral body and anterior vertebral body for spinal metastases using a single field
Other	Cost analysis for different radiotherapy techniques and fractionations may be recommended as part of a clinical trial

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William Hartsell, M.# ...tional Bone

Table 1. Response categories

Term	Definition
Complete response	A pain score of 0 at treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent [OMED])
Partial response	Pain reduction of 2 or more at the treated site on a scale of 0 to 10 scale without analgesic increase, or Analgesic reduction of 25% or more from baseline without an increase in pain.
Pain progression	Increase in pain score of 2 or more above baseline at the treated site with stable OMED, or An increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline

* New addition to the previous consensus response categories.

Table 2. Updated consensus guideline

	Updated consensus guideline
Pain and Analgesic Assessment	Assessment of p... 10, with boun... pain and 10 re... Options for patie... clinic visits, m... telephone inte... tallying, where... Incorporation of ... instruments sp... such as the EO... QLQ-C15-PAL... clinical trials In addition to pa... whether in per... from caregiver... healthcare pro... allowed if nec... Pain should be as... score for the p... Net pain relief ma... evaluating abs... and changes i...
Response Guideline	Reirradiation of ... should only be... completion of the initial treatment course A response category termed "indeterminate response" is recommended, representing response other than complete or partial response and pain progression

	Updated consensus guideline
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	...st analysis for different radiotherapy techniques and fractionations may be recommended as part of a clinical trial

Radiation Therapy:

- Radiation therapy can be used to treat painful bone metastases refractory to systemic therapies
  - 80-90% of cancer patients experience relief of symptoms
  - 40-46% experience full relief *Tong et al, Cancer 1982*

Studies	CR		PR		Reference
	Multiple Fractions	Single Fraction	Multiple Fractions	Single Fraction	
Chow et al, 2004	21%	25%	26%	30%	Support Cancer Ther 2004;1:173–178
Hartsell et al, 2005	11%	17%	31%	49%	J Natl Cancer Inst 2005;97:798–804
Van Der Linden et al, 2004	13%	14%	68%	72%	Int J Radiat Oncol Biol Phys 2004;59:528–537
Foro et al., 2008	13%	11%	51%	52%	Radiother Oncol 2008;89:150–155

What lesson can we learn ?

The adoption of the stricter criteria have resulted in lower complete and partial response rates when compared with those traditionally reported in randomized RT trials.

The decrease in response rates can be more reflective of true response to RT, as the 2002 guideline incorporated analgesic intake in the endpoint definitions, whereas reporting this was not commonplace before the 2002 consensus

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DOI 10.1007/s00330-011-2133-3

ONCOLOGY

A feasibility study of percutaneous radiofrequency ablation followed by radiotherapy in the management of painful osteolytic bone metastases

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Abstract

Objectives To determine whether Radiofrequency Ablation (RFA) followed by Radiotherapy (RT) (RFA-RT) produces better palliation in terms of pain than RT alone in patients with osteolytic bone metastases.

Methods Patients with solitary bone metastases and a pain score of least 5 or more on the VAS scale were selected. Fifteen patients were treated with RFA-RT (20 Gy delivered in 5 fractions of 4 Gy over 1 week) and were compared with a matched group (30 subjects) treated by RT.

Results A complete response in terms of pain relief at 12 weeks was documented in 16.6% (5/30) and 53.3% (8/15) of the subjects treated by RT or RFA-RT, respectively (p=0.027). The overall response rate at 12 weeks was 93.3% (14 patients) in the group treated by RFA-RT and 59.9% (18 patients) in the group treated by RT (p=0.048). Although recurrent pain was documented more frequently after RT (26.6%) than after RFA-RT (6.7%) the difference did not reach statistical significance. The morbidity related to RT did not significantly differ when this treatment was associated with RFA.

Conclusions Our results suggest that RFA-RT is safe and more effective than RT. The findings described here should serve as a framework around which to design future clinical

Study Aim

To investigate whether the addition of radiotherapy (RT) to cryoablation (CA) favorably affects clinical management of painful bone metastases compared with CA and RT delivered as individual treatments.

Study endpoints and response criteria

The primary endpoints :

(1) complete (CR) at 12 weeks after treatments

(2) partial response (PR) at 12 weeks after treatments.

The secondary endpoints :

(1) the rate of subjects requiring analgesics at 12 weeks after treatments

(2) the changes in self-experienced QoL at 12 weeks after treatments

Selection criteria

1. Radiological and histological confirmed painful solitary bone metastases

2. A pain score of 5 or more on the validated visual analog scale (VAS) over the prior 24 hours (or a score of less than 5 with the use of narcotic medications)

3. Pain localized to the site of the bone metastases

4. Life expectancy of greater than 3 months

5. Karnofsky performance status (KPS) score of greater than 70

Exclusion criteria

1. A painful area previously treated with RT or palliative surgery

2. Radiographic evidence of spinal cord or cauda-equina compression

4. Abnormal fracture of the treatment site

3. Lesions positioned within 0.5 cm from a critical structure such as the spinal cord, brain, aorta, inferior vena cava, bowel, or bladder

Treatment modalities

1. Radiation treatment (20 Gy in five fractions of 4 Gy over 1 week)

2. CT guided Cryoablation

3. CT guided Cryoablation followed by RT 15 days later when technically feasible

Statistical Methods

Determination of Sample Size

The primary null hypothesis of this feasibility study was that, for patients with painful bone metastasis, pain relief achieved following CA-RT should be higher than that achieved following RT alone. **The current study was powered to determine an increase of 26% or greater in the CR at 12 weeks after CA-RT with respect to RT alone**. The literature indicates that from 11 to 21% of intention-to-treat (ITT) patients achieved CR after RT. [30] Thus, we set the rate of CR after RT at 11% (P0=11%). Using a two-sided test and a 5% type I error adjusted for Bonferroni correction ($p<0.0166$), with the matched control to case ratio of 1:5, 25 subjects in the experimental groups (CA group and CA-RT group) and 125 in the control group (RT) would provide greater than 80% power to detect an increase of 29% (P1=40%).

Statistical Methods

Key features of propensity score analyses

Design	When to use	Advantages	Disadvantages
Randomization	Whenever feasible When there is variation at the individual or community level	Gold standard Most powerful	Not always feasible Not always ethical
Randomized Encouragement Design	When an intervention is universally implemented	Provides exogenous variation for a subset of beneficiaries	Only looks at sub-group of sample Power of encouragement design only known ex post
Regression Discontinuity	If an intervention has a clear, sharp assignment rule	Project beneficiaries often must qualify through established criteria	Only look at sub-group of sample Assignment rule in practice often not implemented strictly
Difference-in-Differences	If two groups are growing at similar rates Baseline and follow-up data are available	Eliminates fixed differences not related to treatment	Can be biased if trends change Ideally have 2 pre-intervention periods of data
Matching	When other methods are not possible	Overcomes observed differences between treatment and comparison	Assumes no unobserved differences (often implausible)

Table 2 **Some typical steps of propensity analysis, exemplified by the observational study of Ahmed *et al.*[17]**

Step	Task	Method used in example
1	Identify confounding variables	19 relevant covariates measured at baseline
2	Estimate propensity scores as the probability of receiving experimental treatment	Logistic regression of diuretic treatment (yes/no) at baseline on 19 covariables including clinically meaningful interactions
3	Match experimental to control patients	Matching algorithm: '5 to 1 digit matching on propensity score'
4	Evaluate success of matching	Compute standardized differences, compare with values before matching
5	Compare outcome measures of treatment groups	Cox regression stratified for matched pairs, adjustment for confounding variables
6	Interpretation	'No-diuretic patients have 1.3-fold mortality compared with diuretic patients with equal baseline characteristics'

Table 1. Clinical characteristics according propensity score

Characteristics	RT (n=125)	CA-RT (n=25)	CA (n=25)	p value
Age, Y*	68 (66 to 69)	69 (65 to 71)	67.5 (64.4 to 70.6)	0.454°
VAS Scale*	7 (6 to 7)	7 (6 to 8)	7.5 (5 to 7.6)	0.766°
Sex, No (%)				
Male	61 (48.8)	13(52)	12(48)	0.950°°
Famale	64 (51.2)	12 (48)	13 (52)	
KPS, No				
91-100	64 (51.2)	12 (48)	11 (44)	0.908°*
70-89	61 (48.8)	13 (52)	14 (56)	
Tumor Size, cm (longest diameter)	4 (4 to 5)	5 (4 to 5)	4 (3.4 to 6)	0.099°
Primary Tumors, No (%)				
Lung Cancer	38 (30.4)	6 (24)	6 (24)	0.940°*
Prostate Cancer	41 (32.8)	8 (32)	8 (32)	
Renal Cancer	9 (7.2)	2 (8)	4 (16)	
Colorectal Cancer	8 (6.4)	2 (8)	2 (8)	
Breast Cancer	29 (23.2)	7 (28)	5 (20)	
Metastasis Location, No (%)				
Pelvis	52 (41.6)	9 (36)	8 (32)	0.961°*
Sacrum	29 (23.2)	6 (24)	7 (28)	
Rib	10 (8)	2 (8)	2 (8)	
Vertebrae	22 (17.6)	4 (16)	4 (16)	
Humerus	9 (7.2)	2 (8)	2 (8)	
Femur	3 (2.4)	2 (8)	2 (8)	
Characteristics				p value
Medical Systemic Treatments **				
Bisphosphonates	RT (n=125)	CA-RT (n=25)	CA (n=25)	0.701°°
Narcotic Analgesics	35 (28)	9 (36)	8 (32)	1.0°*
Hormonal Therapy	125 (100)	25 (100)	25 (100)	0.888°°
Chemotherapy	34 (27.2)	7 (28)	8 (32)	0.745°*
	80 (64)	16 (64)	15 (60)	0.023°°
	9 (7.2)	2 (8)	4 (12)	

QUESTION 1

Does Cryoablation followed by RT result in improved CR and PR?

Table 2. Response rate following Radiotherapy vs Cryoablation vs Cryoablation combined with Radiotherapy at 12 weeks

Response type No (%)	RT (N=125)	CA (N= 25)	CA-RT (N= 25)	°Pairwise Comparisons p value
Complete response (No, %)	14/125 (11.2)	8/25 (32)	18/25 (72)	CA vs RT p=0.018 CA vs CA-RT p= 0.011 CA-RT vs RT p<0.0001
Partial Response (No,%)	53/125 (42.4)	9/25 (36)	3/25 (12)	CA vs RT p=0.711 CA vs CA-RT p= 0.098 CA-RT vs RT p=0.008
Stable Pain or Progression (No,%)	58/125 (46.4)	8/25 (32)	4/25 (16)	CA vs RT p=0.270 CA vs CA-RT p= 0.321 CA-RT vs RT p=0.009

°Chi Square test or Fisher exact test. In post hoc pairwise comparisons of subgroups the alpha error was set at 0.016 according to Bonferroni correction; RT= radiotherapy; CA-RT= Cryoablation-Radiotherapy;

QUESTION 2

Does Cryoablation followed by RT result in reduced requirement of analgesic use ?

Results

Table 3. Post-treatment narcotic analgesic use and morphine equivalent dose at 12 weeks

Narcotic medications	RT (N=125)	CA (N= 25)	CA-RT (N= 25)	Pairwise Comparisons p value
None (No, %)	17 (13.6)	9 (36)	19 (76)	°CA vs RT p=0.016 °CA vs CA-RT p= 0.010 °CA-RT vs RT p<0.0001
Required (No,%)	108 (86.4)	16 (64)	6 (24)	

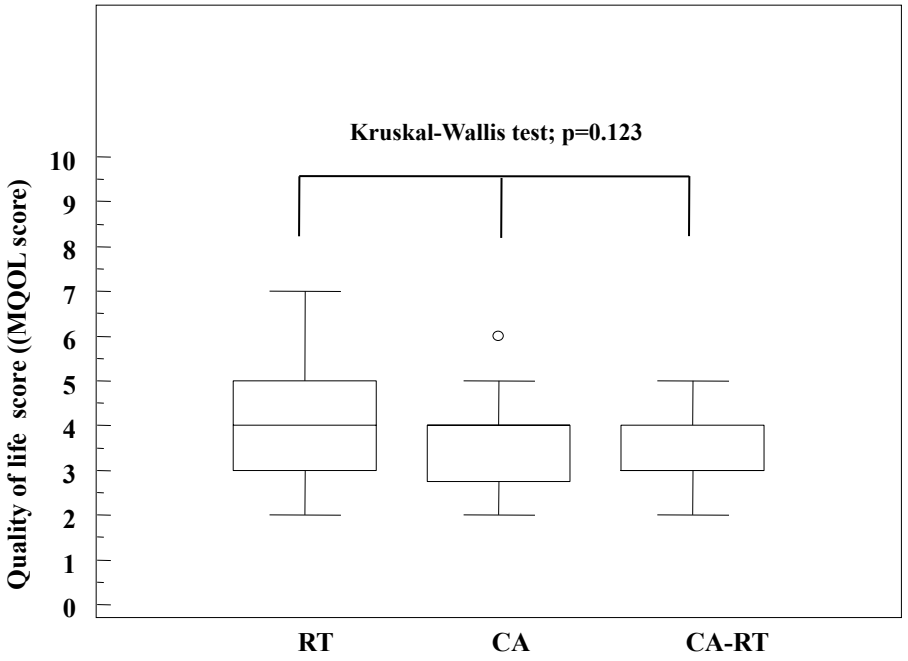
°Chi Square test; RT= radiotherapy; CA-RT= Cryoablation-Radiotherapy; °° Kruskal Wallis test with post hoc pairwise comparison of subgroups performed according to Conover; °* median and CI95%.

QUESTION 2

Does Cryoablation followed by RT affect the quality of life?

Results

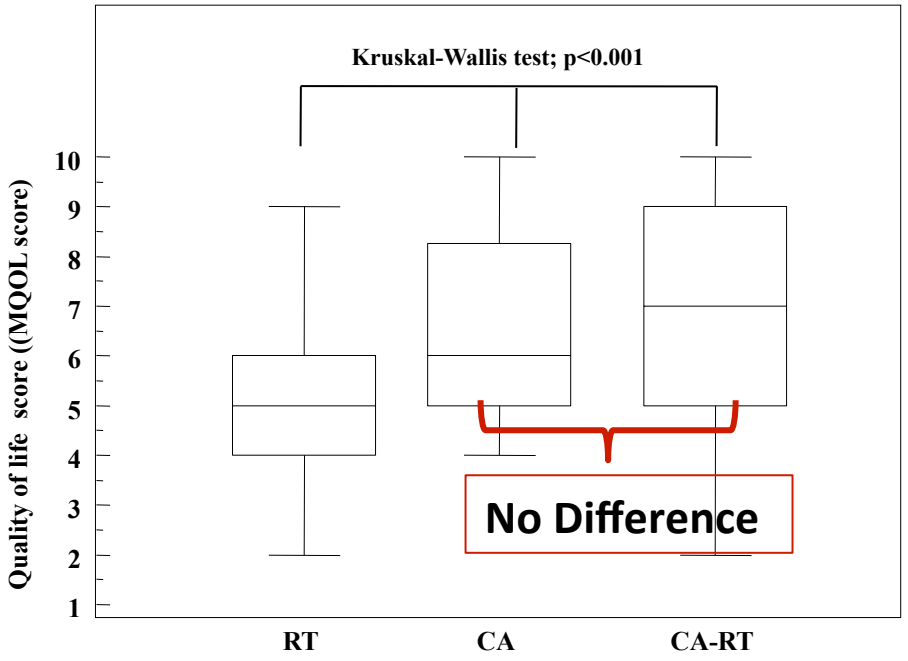
Self-rated QoL (Baseline)



Groups	N	Average Rank	Pairwise comparisons* (p<0.05)
RT	125	92,80	No significant difference
CA	25	77,66	No significant difference
CA-RT	25	74,36	No significant difference

* Kruskal-Wallis test with Pairwise comparisons according to Conover.

Self-rated QoL (Week 12)



Groups	N	Average Rank	Pairwise comparisons* (p<0.05)
RT	125	75,96	CA; CA-RT
CA	25	115,26	RT
CA-RT	25	120,92	RT

* Kruskal-Wallis test with Pairwise comparisons according to Conover.

Results

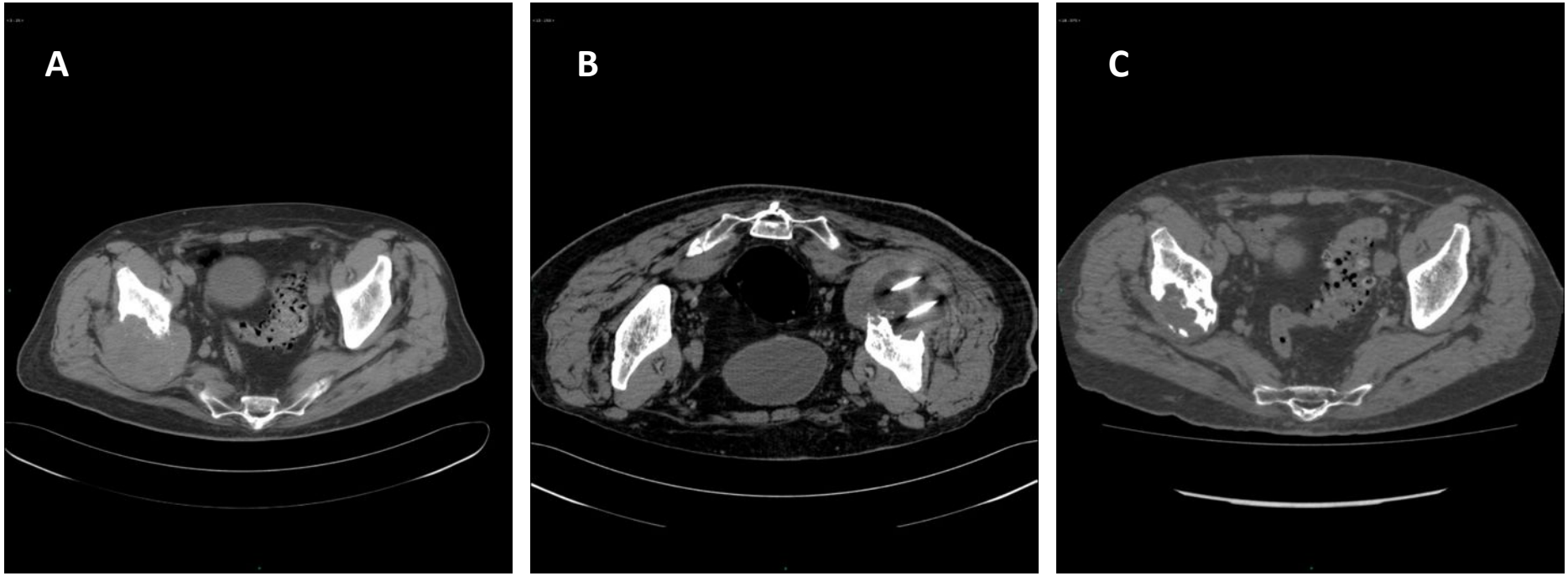


Figure 2

Conclusions

- Metastatic bone disease is an important healthcare problem
- Currently available treatments have a limited range of activity
- CA when combined with radiotherapy may result in complete response in terms of pain control and improve self-rated quality of life.
- Our preliminary results have to be interpreted with caution and to serve as a framework around which to design future large-scale RCT.