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BONE METASTASES | CLINICAL REVIEW

Bone is the third most common site of metastases (after lung and liver) with breast, prostate, lung, thyroid, bladder, and renal cell cancers accounting for the majority of skeletal metastases[1]

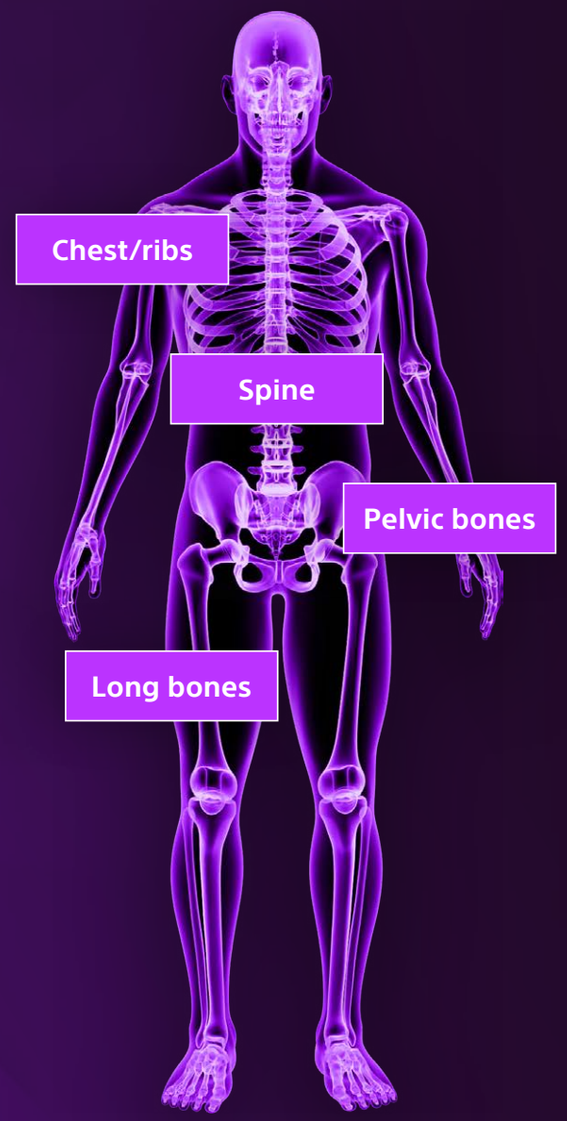
An estimated **382,733 patients with bone metastases** in the U.S. compared to 3,450 cases of primary bone cancer [2,3]

Bone metastases are a leading cause of morbidity for cancer patients including significant pain, fractures, spinal cord compression, and impaired mobility[1,4]

Approximately 80% of patients with bone metastases have bone-related pain[4,5]

Femur is the most common long bone affected by metastatic cancer and accounts for nearly 25% of all bony metastases

Main sites of bone metastases include[1]:



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PAIN PALLIATION I INTRODUCTION

- **Painful bone metastases are the most common source of pain from cancer.**
  - One of the hallmarks of the bone pain is that it often is increased at night
- Different sites of bone metastases have specific pain profiles
  - Vertebral metastases with associated neck and back pain with or without neurological complications secondary to epidural extension
  - Pelvic and femoral lesions are associated with back and lower limb pain and mechanical instability[6].
- Treatment decisions depend on several parameters, including whether highly localization or extensive metastases, extra-skeletal metastases, type of cancer, response to previous treatments, symptoms, and overall morbidity[1].
- Multidisciplinary teams (including a medical oncologist, surgeon, interventional radiologist, radiation oncologist, and pain management physician) are essential for managing the complexities of the varied treatments that patients with bone metastases often receive over the course of the disease.
- Painful bone metastasis reduces the QoL of patients with cancer.

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PAIN PALLIATION I TREATMENT OPTIONS

- The varied treatments have different benefits, including partial response, onset and duration of pain palliation
  - Important to consider side effects of treatments which impact future treatment decisions
- Radiation is the standard of care for painful bone metastases with most of the patients prescribed chemotherapy and opioids at some point during the course of the disease
- Pharmaceutical treatments
  - Analgesics (NSAIDs, opioids, corticosteroids)
  - Bone modifying agents (bisphosphonates, densomab)
  - Directed therapies (chemotherapies, hormonal therapy, immunotherapies)
- Interventional treatments
  - Radiotherapy – Standard of Care
  - Ablation (Cryoablation, Radiofrequency, MRI-guided Ultrasound, and Microwave)
  - Embolization
  - Cementoplasty
  - Surgery
  - Neuromodulation/nerve blocks

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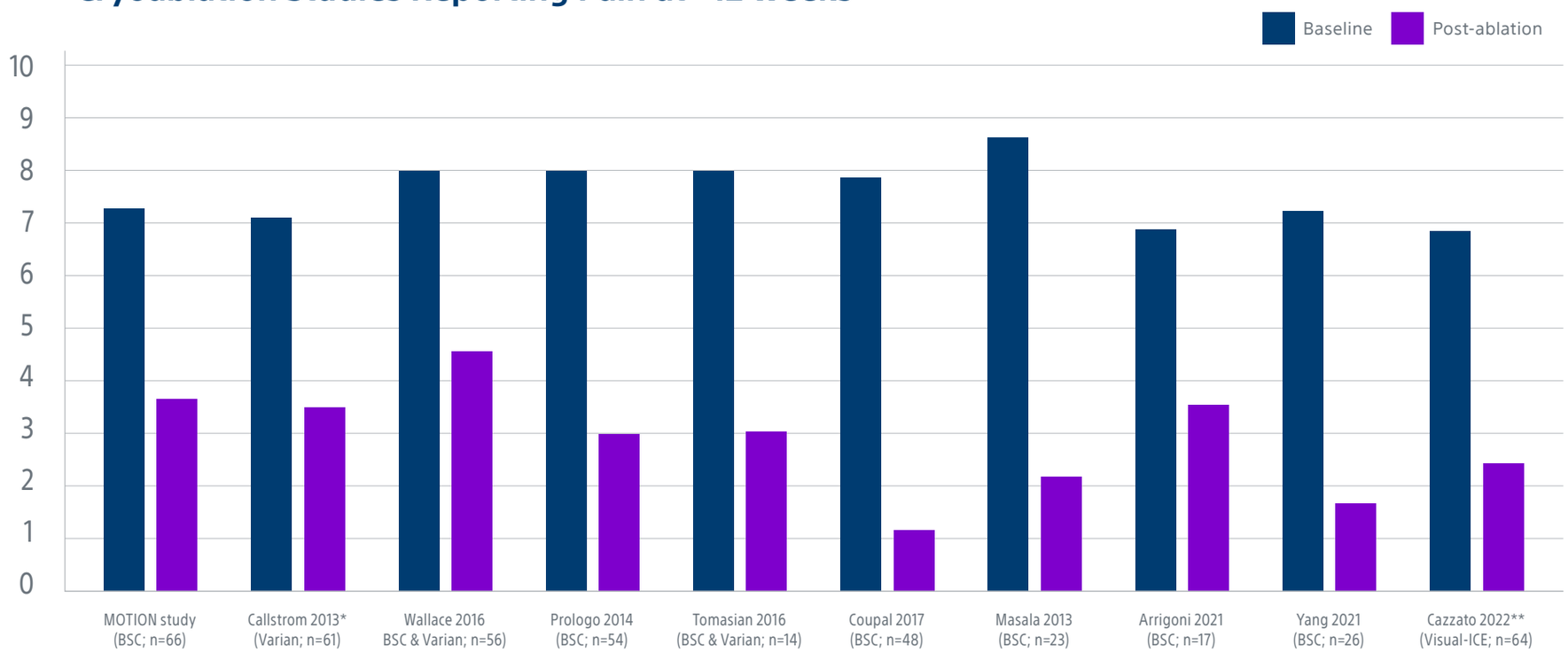
PAIN PALLIATION I KEY STUDIES

Cryoablation Studies Reporting Pain at ~12 weeks



Significant decrease in pain from baseline to 12 Weeks. Studies reporting outcomes from 381 patients following cryoablation of bone metastases on a 10-Point scale showing; * Callstrom et al closest time point reported was 8 weeks; ** Cazzato et al closest time point reported was 24 weeks

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PAIN PALLIATION I KEY STUDIES

The MOTION Multicenter Study I Cryoablation for Palliation of Painful Bone Metastases

Title	Cryoablation for Palliation of Painful Bone Metastases: The MOTION Multicenter Study
Type of Study	Multi-center, prospective, single arm, phase II study (11 sites; 4 EU and 7 US)
Number of patients	66
Pain Reduction Outcome	Primary Endpoint of Worst pain score in 24 hours at 8 weeks: -2.61 ± 0.43 points (95% CI: -3.45, -1.78)
Opioid Reduction Outcome	MEDD among complete-case participants decreased from week 4 to week 24
QOL Improvement Outcome	Quality of life assessment demonstrated improvements from weeks 1 to 24
Approach & Protocol	Standard cryoablation protocol including two freeze-thaw cycles. Freeze duration varied to encompass the entire tumor or as much of the tumor as could be safely treated.

Significant decrease in pain from baseline to 12 Weeks. Studies reporting outcomes from 381 patients following cryoablation of bone metastases on a 10-Point scale showing; * Callstrom et al closest time point reported was 8 weeks; ** Cazzato et al closest time point reported was 24 weeks

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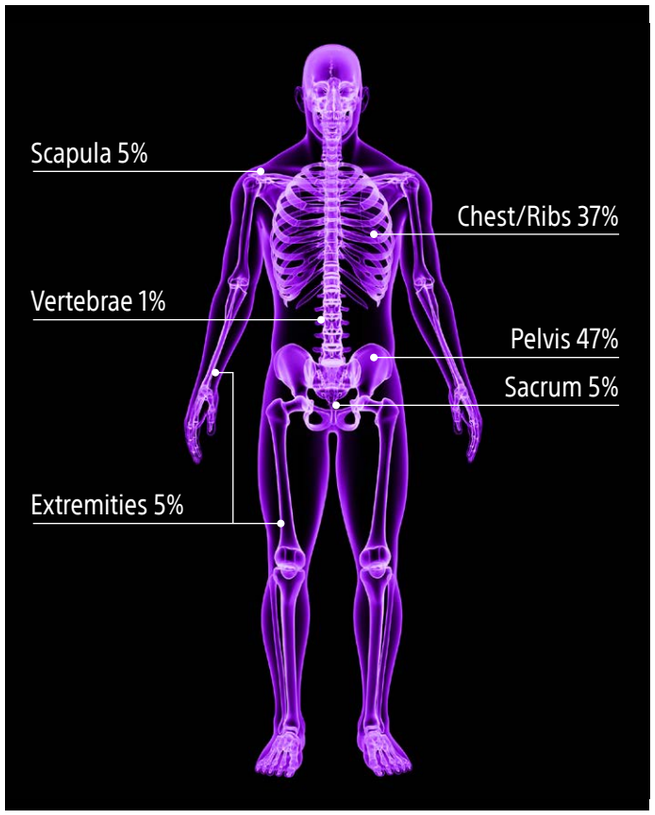
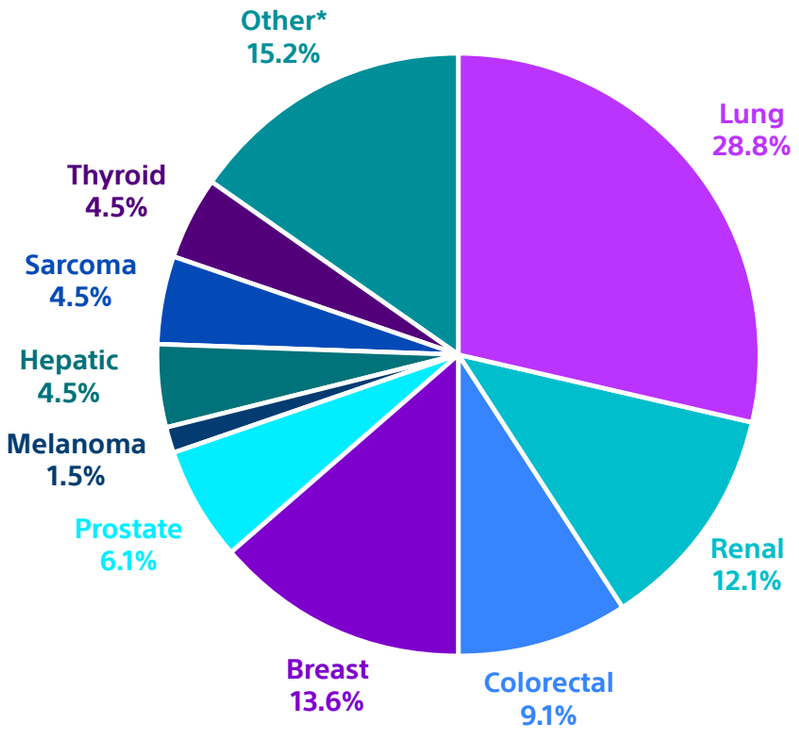
PAIN PALLIATION I KEY STUDIES

The MOTION Multicenter Study I Index Tumor Characteristics

Target Lesion Location



Tumor Type



Jennings J, et al., Radiology: Imaging Cancer 2021; 3(2):e200101

*Other types (≤4% each including stomach, other GI, bladder, uterine, urothelial, urachus, penile, unknown)

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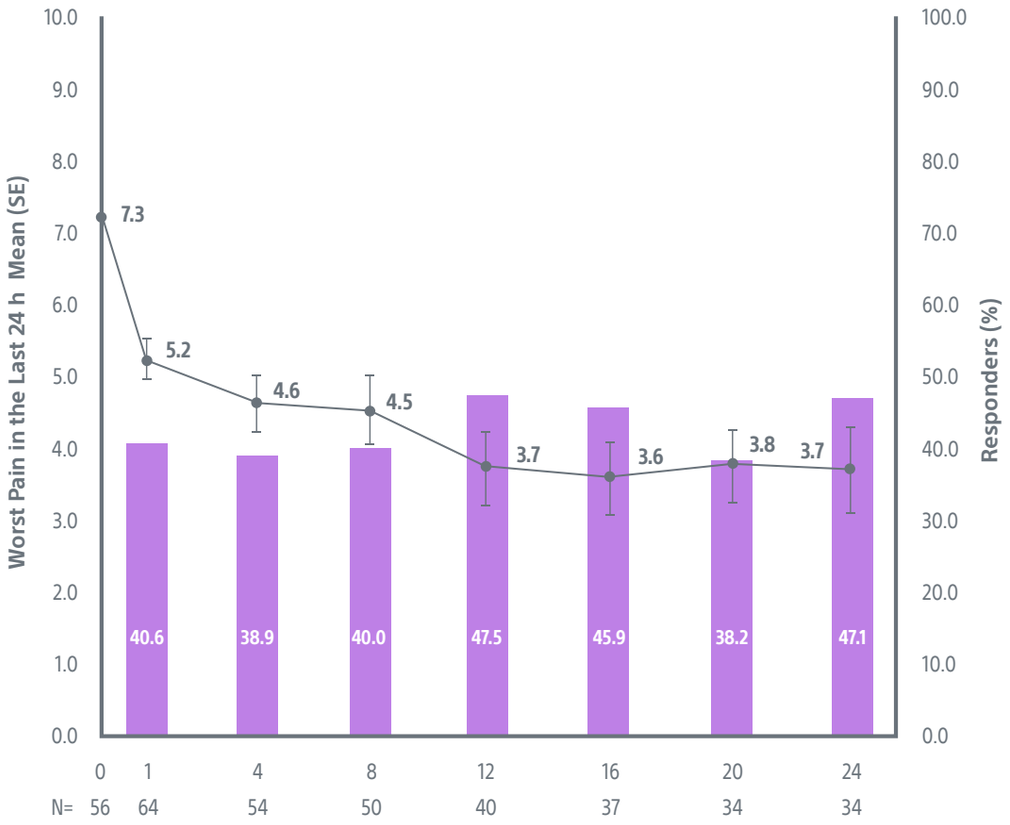
PAIN PALLIATION I KEY STUDIES

The MOTION Multicenter Study I Worst Pain in Last 24 Hours



Primary Endpoint:

- Worst pain score in 24 hours at 8 weeks
  -2.61 ± 0.43 points
  (95% CI: -3.45, -1.78) at Week 8

- Clinically meaningful change in pain scores **at Weeks 12, 16, 20, and 24**
- 92% (59/64) of patients achieved pain palliation

- **Max Pain Palliation**
  33.9% @ Week 1
  25.4% @ Week 4
  15.3% @ Week 12

Jennings J, et al., Radiology: Imaging Cancer 2021; 3(2):e200101

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PAIN PALLIATION I KEY STUDIES

The MOTION Multicenter Study I Safety

Safety and Adverse Events	Participants (n=45)
Possibly related adverse events	14 (22)%
Hematoma	2 (3.1%)
Nausea	2 (3.1%)
Tumor pain	2 (3.1%)
Other	5 (7.7%)
Hypotension	1 (1.5%)
Pain at needle site	1 (1.5%)
Pleural effusion	1 (1.5%)
Frostbite/skin burn	1 (1.5%)
Vomiting	1 (1.5%)
Serious Adverse Events	3 (4.6)%
Abdominal pain	1 (1.5%)
Hematoma	1 (1.5%)
Frost bite (Grade 4)	1 (1.5%)

Jennings J, et al., Radiology: Imaging Cancer 2021; 3(2):e200101

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PAIN PALLIATION I KEY STUDIES

Callstrom MR, et al, 2013 I Percutaneous Image-Guided Cryoablation of Painful Metastases Involving Bone

Title	Percutaneous Image-Guided Cryoablation of Painful Metastases Involving Bone
Type of Study	Multi-center, prospective, single arm, phase II study (8 US sites)
Number of patients	61
Pain Reduction Outcome	Primary Endpoint of Worst pain in 24 hours and avg pain at 8 weeks: Worst pain @ 8 weeks: 3.6 (0.0001); Avg. pain @ 8 weeks: 2.1 (0.0001)
Opioid Reduction Outcome	83% of patients (39 of 47) reported a reduction in the use of opioid analgesic medications
QOL Improvement Outcome	67% (41/61) of patients over the study experienced at least a 2-point reduction in mean score for interference of pain on activities of daily living
Approach & Protocol	10 Minute Freeze > 8 Minute Passive Thaw > 10 Minute Freeze

Callstrom MR, et al., Cancer 2013 Mar 1;119(5):1033-41

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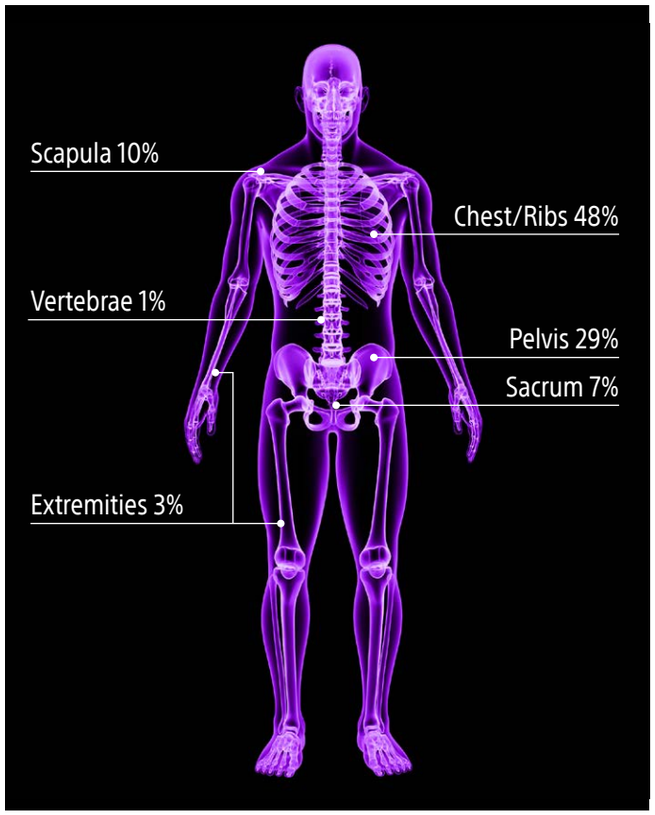
PAIN PALLIATION I KEY STUDIES

Callstrom MR, et al, 2013 I Index Tumor Characteristics

Target Lesion Location (n=69*)



Tumor Type

* N=69 lesions in 61 patients (8 patients with 2 tumors 53 patients with single tumors)
Callstrom MR, et al., Cancer 2013 Mar 1;119(5):1033-41

**other types not detailed

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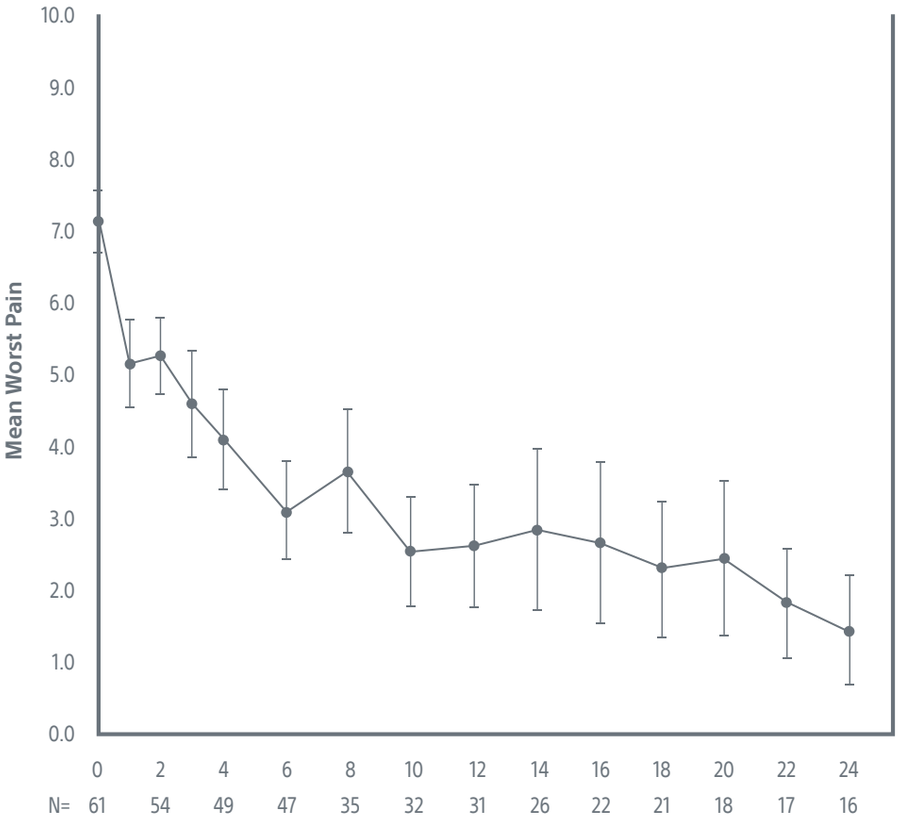
PAIN PALLIATION I KEY STUDIES

Callstrom MR, et al, 2013 I Percutaneous Image-Guided Cryoablation of Painful Metastases Involving Bone



Callstrom MR, et al., Cancer 2013 Mar 1;119(5):1033-41

Primary Endpoint:

- Worst pain in 24 hours and average pain scores on a visual analogue scale, using a score of 0 to 10 from baseline to week 8

Worst pain @ 8 weeks: 3.6 ($p<0.0001$)
Avg. pain @ 8 weeks: 2.1 (0.0001)

- From baseline to week 1:
  - 49% of patients (30 of 61) reported at least a 2-point decrease in worst pain
  - 30% of patients (24 of 61) reporting at least a 3-point drop in worst pain
- 75% of patients (46 of 61) reported 90% or higher pain relief at some time in the follow-up period

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PAIN PALLIATION I KEY STUDIES

Callstrom MR, et al, 2013 I Safety

- One of 61 (2%) patients had a major complication with osteomyelitis at site of ablation
  - Developed an infection in the treated area 2 weeks after treatment subsequently treated with intravenous antibiotics and surgery
- No instances of moderate or severe complication due to injury of major motor nerves, bowel, or bladder

Callstrom MR, et al., Cancer 2013 Mar 1;119(5):1033-41

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PAIN PALLIATION I VERTEBRAL METASTASES

Tomasian A, et al., 2016 I Spine Cryoablation: Pain Palliation and Local Tumor Control for Vertebral Metastases

Title	Spine Cryoablation: Pain Palliation and Local Tumor Control for Vertebral Metastases
Type of Study	Single center, retrospective, single arm, phase II study
Number of patients	14 patients with 31 painful bone metastases
Pain Reduction Outcome	Pain reduced from 8 ± 1 pre-procedure to 3 ± 1at 1-week, 1-month, and 3-months post-procedure (0.0001)
Opioid Reduction Outcome	Narcotic use decreased from 360 ± 105 mg at baseline to 80 ± 45 mg @ 3 months (p<0.001)
Local Control Outcome	Demonstrated 96.7% (30/31) local control post cryoablation @ median of 10 months
Approach & Protocol	10 Minute Freeze > 5 Minute Active Thaw > 10 Minute Freeze

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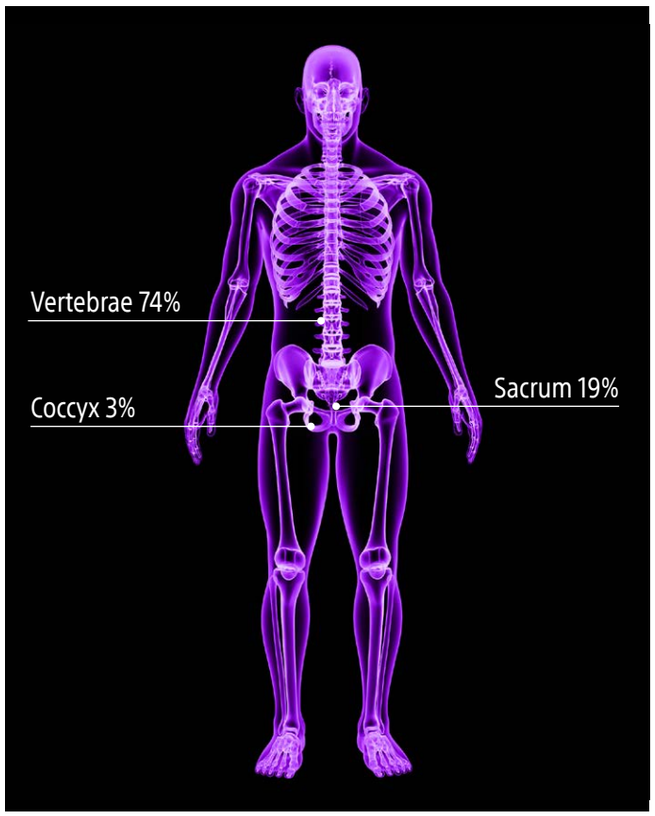
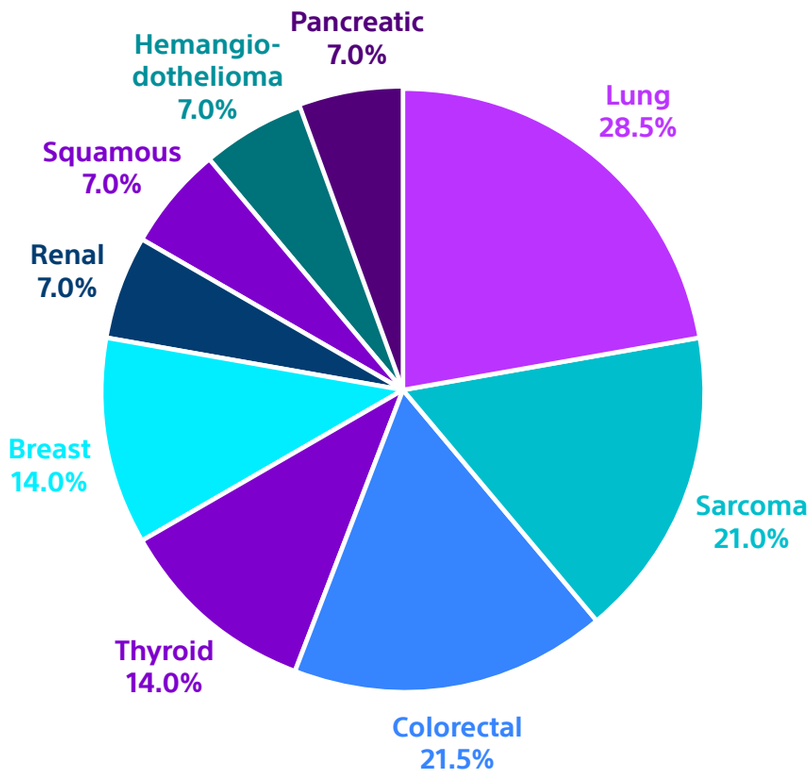
PAIN PALLIATION I VERTEBRAL METASTASES

Tomasian A, et al., 2016 I Index Tumor Characteristics

Target Lesion Location (n=31*)



Tumor Type



* N=with 31 tumors in 14 patients
Tomasian A, et al., Am J Neuroradiol 2016; 37:189–195

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PAIN PALLIATION I VERTEBRAL METASTASES

Tomasian A, et al., 2016 I Pain Palliation and Safety

Pain Palliation:

- Decreased pain from baseline median of 8.1 through 3 months
  - Median pain @ 1 week: 3.1 ± 1 (p<0.001)
  - Median pain @ 1 month: 3.1 ± 1 (p<0.001)
  - Median pain @ 3 months: 3.1 ± 1 (p<0.001)

Safety:

- Procedural complication rate was 14.3% (2/14)
- 2 minor complications - postprocedural radicular lower extremity nerve pain

Tomasian A, et al., Am J Neuroradiol 2016; 37:189–195

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PAIN PALLIATION I VERTEBRAL METASTASES

Masala S, et al., 2013 I Spine Cryoablation + Vertebroplasty vs. Vertebroplasty

Title	Combined use of percutaneous cryoablation and vertebroplasty with 3D rotational angiograph in treatment of single vertebral metastasis: comparison with vertebroplasty
Type of Study	Single center, retrospective, single arm, phase II study
Number of patients	46 (23 Cryo + VT and 23 VT)
Pain Reduction Outcome	VAS scores showed statistically significant difference between patients treated with CVT and patients managed with VT at all follow-up visits treatment ($p<0.001$)
Quality of Life Outcome	Quality of Life scores showed a statistically significant difference between patients treated with CVT and patients managed with VT ($p<0.001$)
Approach & Protocol	10 Minute Freeze > 5 Minute Active Thaw > 10 Minute Freeze

Masala S, et al., Neuroradiology 2013; 55:193–200

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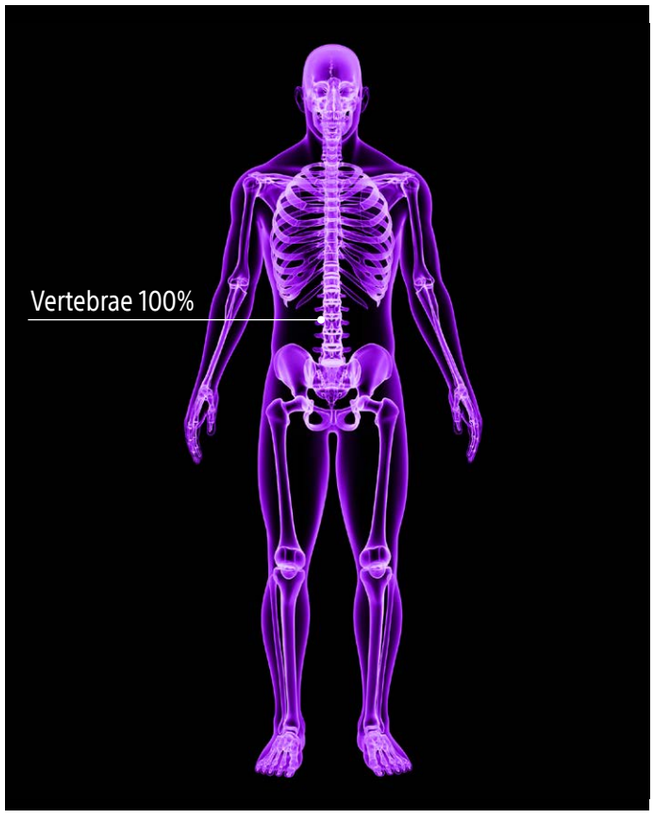
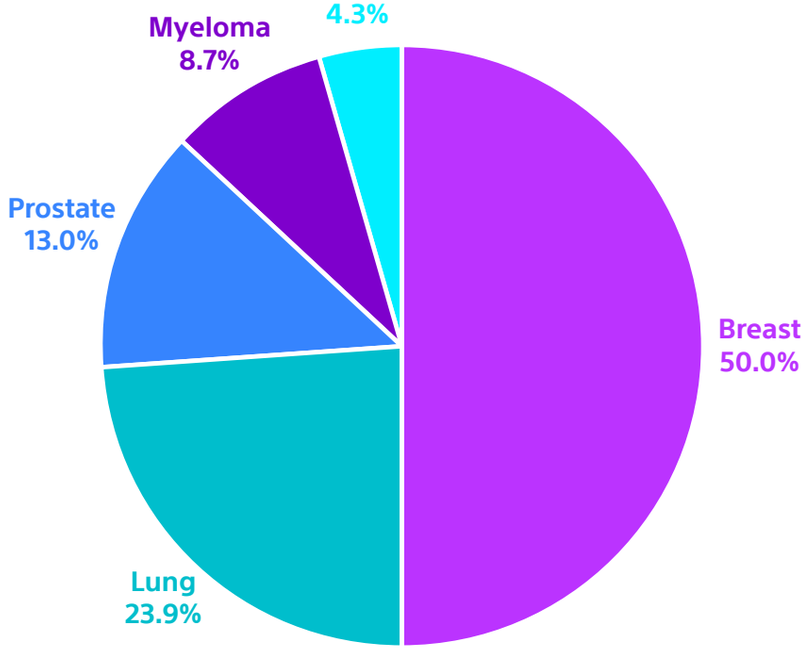
PAIN PALLIATION I VERTEBRAL METASTASES

Masala S, et al., 2013 I Index Lesion Characteristics

Target Lesion Location (n=46*)



Tumor Type (n=46)



* N= 46 patients (CVT=23 and VT=23)
Masala S, et al., Neuroradiology 2013; 55:193–200

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PAIN PALLIATION I VERTEBRAL METASTASES

Masala S, et al., 2013 I Pain Palliation and Safety

CVT:

- Decreased pain from baseline mean of 8.6 ± 1.1 through 6 months
  - Mean pain @ 1 week: 2.9 ± 1.2 ($p<0.05$)
  - Mean pain @ 1 month: 2.5 ± 1.0 ($p<0.05$)
  - Mean pain @ 3 months: 2.2 ± 0.9 ($p< 0.05$)
  - Mean pain @ 6 months: 2.1 ± 1.1 ($p< 0.05$)

VT:

- Decreased pain from baseline mean of 8.2 ± 1.3 through 6 months
  - Mean pain @ 1 week: 4.2 ± 1.6 ($p<0.001$)
  - Mean pain @ 1 month: 3.8 ± 1.6 ($p< 0.001$)
  - Mean pain @ 3 months: 3.8 ± 1.4 ($p< 0.001$)
  - Mean pain @ 6 months: 2.1 ± 1.1 ($p< 0.001$)

VAS score showed statistically significant difference between patients treated with CVT and patients managed with VT at all follow-up visits treatment ($p<0.001$)

- 1 week: 2.9 ± 1.2 vs. 4.2 ± 1.6, ($p<0.001$)
- 1 month: 2.5 ± 1 vs. 4.2 ± 1.6, ($p<0.001$)
- 3 months: 2.2 ± 0.9 vs. 3.8 ± 1.4, ($p<0.001$)
- 6 months: 2.1 ± 1.1 vs. 4.2 ± 1, ($p<0.001$)

Safety:

- No procedural complication reported

* N= 46 patients (CVT=23 and VT=23)
Masala S, et al., Neuroradiology 2013; 55:193–200

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PAIN PALLIATION I VERTEBRAL METASTASES

Cazzato RL, et al., 2022 I Percutaneous image-guided cryoablation of spinal metastases: over 10-year experience in two academic centers

Title	Percutaneous image-guided cryoablation of spinal metastases: over 10-year experience in two academic centers
Type of Study	Two center, retrospective, single arm, phase II study
Number of patients	74 patients with 105 lesions
Pain Reduction Outcome	Mean pain score dropped from 6.8 ± 2.2 at the baseline to 4.1 ± 2.4 ($p < 0.0001$) at 24 h, 2.5 ± 2.6 ($p < 0.0001$) at 1 month, and 2.4 ± 2.5 ($p < 0.0001$) at the last available follow-up (mean 14.7 ± 19.6 months; median 6)
Local Control Outcome	At mean 25.9 ± 21.2 months (median 16.5) of follow-up, local tumor control was achieved in 82.1% (23/28) metastases in 21 patients
Approach & Protocol	Cryoablation was generally performed with a double 10-min freeze protocol. For local control, ice ball was required to completely expand beyond borders with minimum margin of 5 –10 mm. For palliation, treatment aimed to ablate the bone-SM interface and whenever technically feasible, the entire metastasis was treated.

Cazzato RL, et al., Eur Radiol 2022; 32:4137–4146

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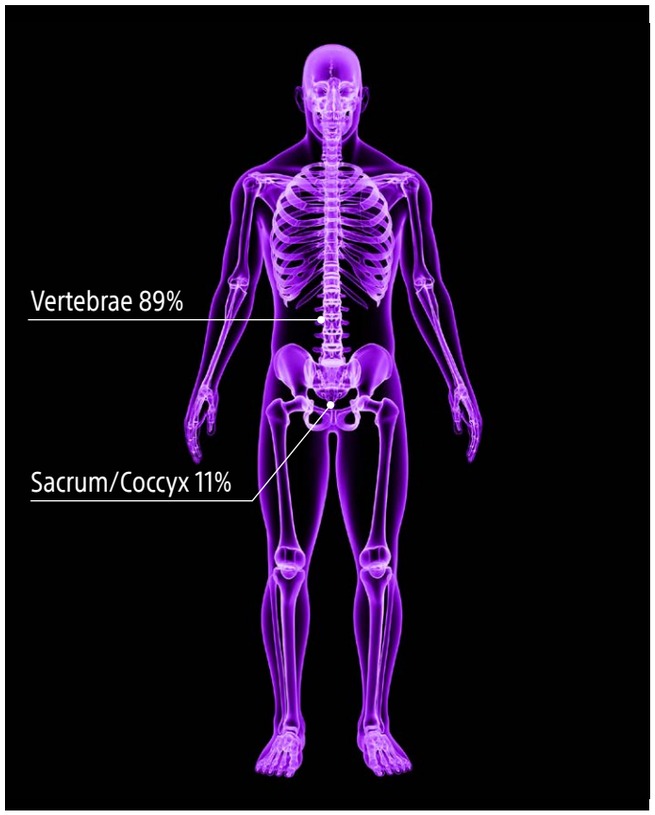
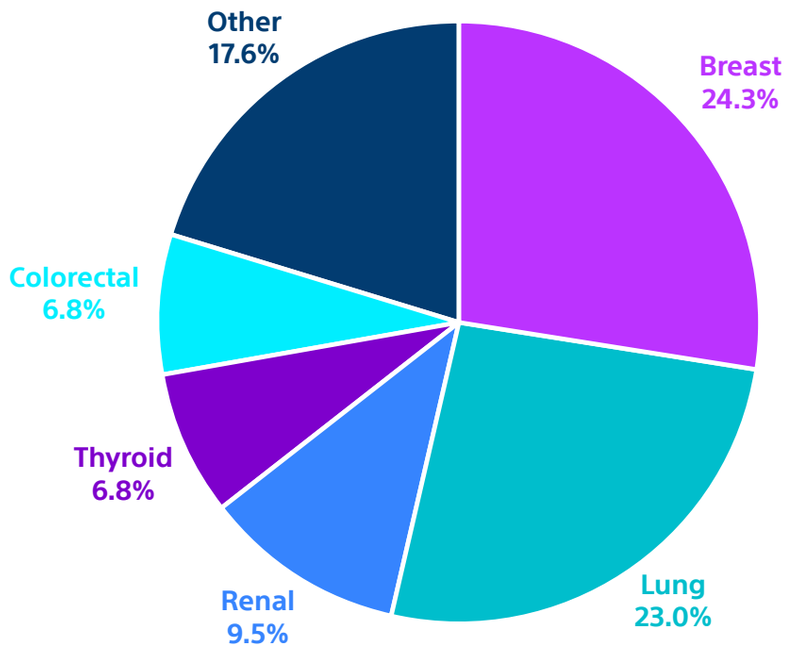
PAIN PALLIATION I VERTEBRAL METASTASES

Cazzato RL, et al., 2022 I Index Tumor Characteristics

Target Lesion Location (n=105*)



Tumor Type (n=105)



* N=74 total patients with 105 tumors
Cazzato RL, et al., Eur Radiol 2022; 32:4137–4146

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PAIN PALLIATION I VERTEBRAL METASTASES

Cazzato RL, et al., 2022 I Pain Palliation and Safety

Pain Palliation:

- Decreased pain from baseline mean of 6.8 ± 2.2 through 14.7 months (mean of last follow up)
  - Mean pain @ 1 day: 4.1 ± 2.4 (p< 0.0001)
  - Mean pain @ 1 month: 2.5 ± 2.6 (p< 0.0001)
  - Mean pain @ 14.7 months: 2.4 ± 2.5 (p< 0.0001)

53.1% patients (34/64) were completely pain-free at last available follow-up

Safety:

- Nine complications (8.6%, 9/105)
- Major (n=2): Third-degree AV block; Postprocedural left lower extremity weakness
- Minor (n=7): Pain, Deficit of the brachial plexus, Left quadriceps weakness, Broken biopsy needle in T1 vertebral body, Right S1 radiculopathy, Left T8 radiculopathy, and Left T9 radiculopathy

* N=74 total patients with 105 tumors
Cazzato RL, et al., Eur Radiol 2022; 32:4137–4146

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PAIN PALLIATION I LARGE PELVIC METASTASES

Coupal TM, et al., 2017 I The Hopeless Case? Palliative Cryoablation and Cementoplasty Procedures for Palliation of Large Pelvic Bone Metastases

Title	The Hopeless Case? Palliative Cryoablation and Cementoplasty Procedures for Palliation of Large Pelvic Bone Metastases
Type of Study	Single center, retrospective, single arm, phase II study
Number of patients	48
Pain Reduction Outcome	Pain decreased from mean pain score of 7.9 at baseline to 1.2 at Day 1 and remained stable at 1 to 9 weeks follow-up (mean: 4.1 weeks; p<0.001). **All lesions >5 cm**
Approach & Protocol	8 Minute Freeze > 6 Minute Active Thaw > 8 Minute Freeze I All patients received cementoplasty

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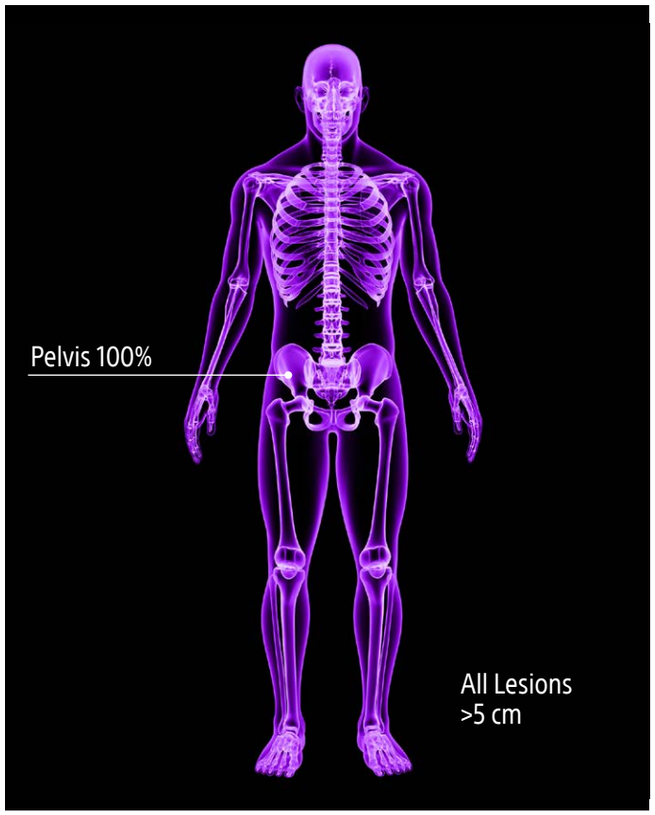
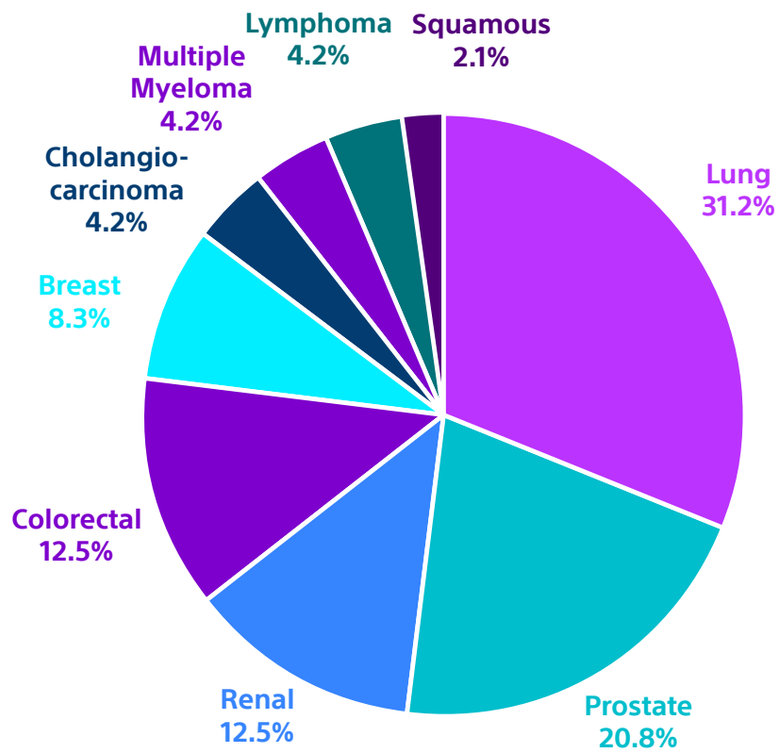
PAIN PALLIATION I LARGE PELVIC METASTASES

Coupal TM, et al., 2017 I Index Tumor Characteristics

Target Lesion Location (n=48)



Tumor Type (n=48)



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Coupal TM, et al., Pain Physician 2017; 20:E1053–E1061

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PAIN PALLIATION I LARGE PELVIC METASTASES

KEY STUDIES		VERTREBRAL			LARGE PELVIC	vs. RFA		vs. RADIATION
MOTION Study	Callstrom 2013	Tomasian 2016	Masala 2013	Cazzato 2022	**Coupal 2017**	Thacker PG 2011	Zugago L 2016	Di Staso M 2015

Coupal TM, et al., 2017 I Pain Palliation and Safety

Pain Palliation:

- Decreased pain from baseline median of 7.9 through ~1 month (range 1-9 weeks)
  - Immediate pain relief - median pain @ 1 day: 1.2 ± ($p<0.001$)
  - No patients reported increased pain
  - 6.3% (3/48) reported no change in pain

Safety:

- No procedural complications

Coupal TM, et al., Pain Physician 2017; 20:E1053–E1061

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PAIN PALLIATION I CRYOABLATION vs. RFA

Thacker PG, et al., 2011 I Palliation of Painful Metastatic Disease Involving Bone With Imaging-Guided Treatment: Comparison of Patients' Immediate Response to Radiofrequency Ablation and Cryoablation

Title	Palliation of Painful Metastatic Disease Involving Bone With Imaging-Guided Treatment: Comparison of Patients' Immediate Response to Radiofrequency Ablation and Cryoablation
Type of Study	Single center, retrospective, dual, phase II study
Number of patients	58 patients: 36 cryoablation and 22 RFA
Pain Reduction Outcome	No differences in baseline (cryo 6.5 ± 2.27; RFA 6.0 ± 1.41; p=0.78), pain 24 hours post ablation (cryo 3.5 ± 2.91; RFA 5.0 ± 2.04; p=0.27), and change in pain (p=0.2)
Opioid Reduction Outcome	Analgesic use 24 hrs pre and post procedure was significantly lower with cryo (median −23.6 ± 137.0; p=0.03) compared with RFA (median 21.6 ± 124.7)
QOL Improvement Outcome	Total hospital length of stay for patients undergoing cryoablation was a median of 2.5 days less than for patients receiving RFA (p = 0.003)
Approach & Protocol	10 Minute Freeze > 8 Minute Thaw > 10 Minute Freeze RFA: 100°C was maintained for a minimum of 5 minutes, with a goal of 5–15 minutes

Thacker PG, et al., AJR 2011; 197: 510-515

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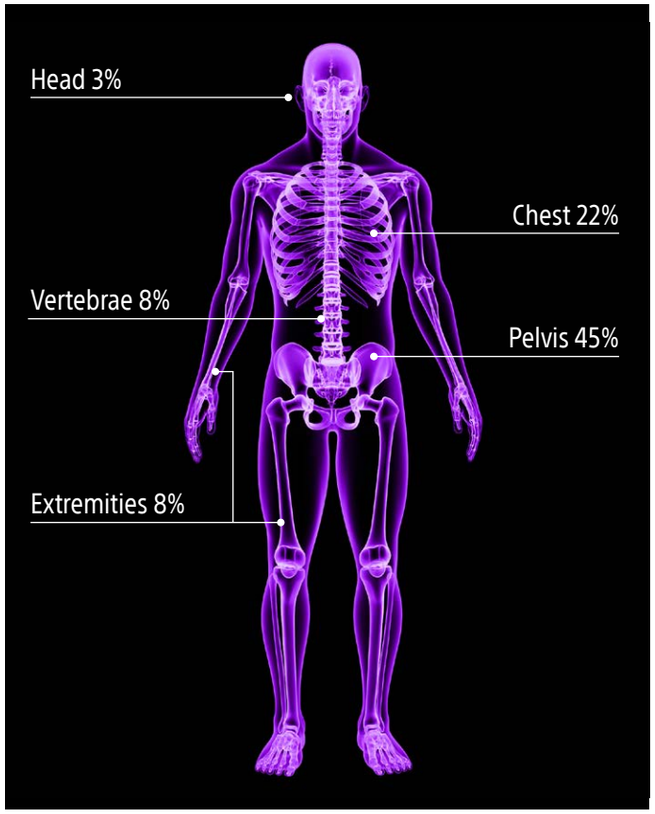
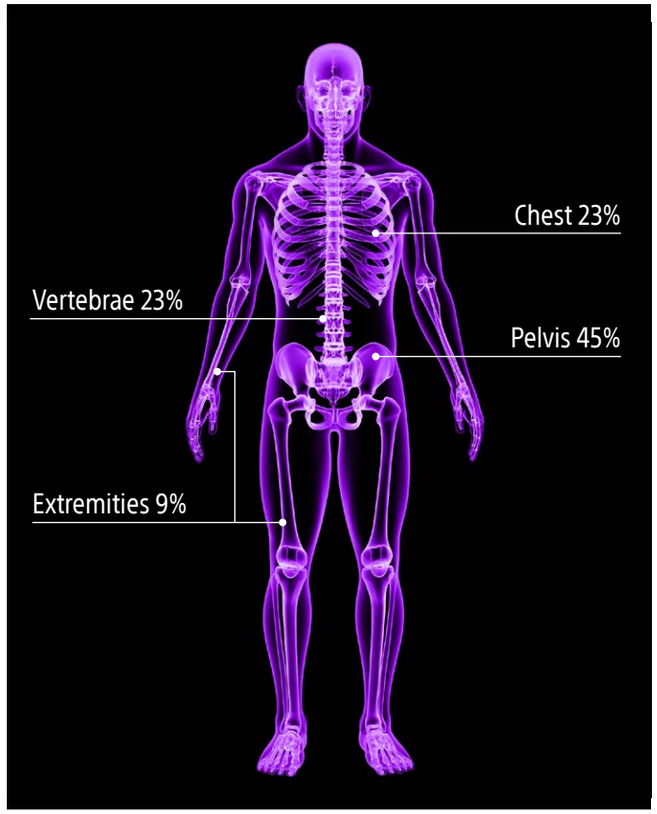
PAIN PALLIATION I CRYOABLATION vs. RFA

Thacker PG, et al., 2011 I Index Tumor Locations

Cryoablation (n=36)



RFA (n=22)



Thacker PG, et al., AJR 2011; 197: 510-515

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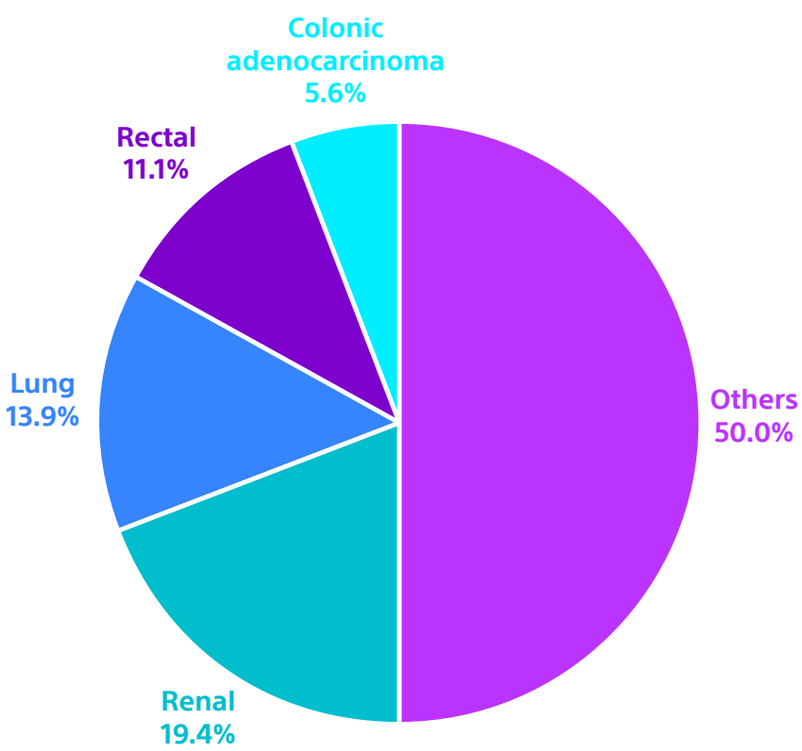
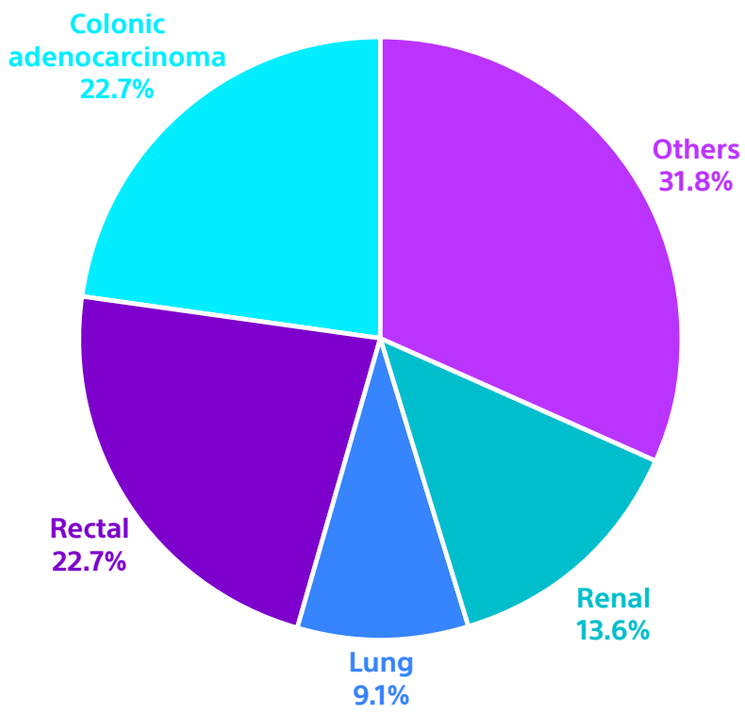
PAIN PALLIATION I CRYOABLATION vs. RFA

Thacker PG, et al., 2011 I Tumor Type

Cryoablation (n=36)



RFA (n=22)



Thacker PG, et al., AJR 2011; 197: 510-515

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PAIN PALLIATION I CRYOABLATION vs. RFA

KEY STUDIES		VERTREBRAL			LARGE PELVIC	vs. RFA		vs. RADIATION
MOTION Study	Callstrom 2013	Tomasian 2016	Masala 2013	Cazzato 2022	Coupal 2017	Thacker PG 2011	Zugago L 2016	Di Staso M 2015

Thacker PG, et al., 2011 I Pain Palliation and Safety

Pain Palliation:

- No differences observed in baseline pain (cryo 6.5 ± 2.27; RFA 6.0 ± 1.41; p=0.78) and pain 24 hours post ablation (cryo 3.5 ± 2.91; RFA 5.0 ± 2.04; p=0.27) and the change in pain (p=0.2)

Safety:

- Two complication from cryo (5.6%, 1/36, temporary S1 vertebra dysesthesia, thermal injury at ablation site) and one complication from RFA (4.5%, 1/22, liver capsule damage)

Thacker PG, et al., AJR 2011; 197: 510-515

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PAIN PALLIATION I CRYOABLATION vs. RFA

Zugago L, et al., 2016 I Treatment of osteolytic solitary painful osseous metastases with radiofrequency ablation or cryoablation: A retrospective study by propensity analysis

Title	Treatment of osteolytic solitary painful osseous metastases with radiofrequency ablation or cryoablation: A retrospective study by propensity analysis
Type of Study	Single center, retrospective, dual, phase II study
Number of patients	50: 25 cryoablation and 25 RFA
Pain Reduction Outcome	A higher proportion of subjects treated by cryo (32%) than RFA (20%) experienced a complete response at 12 weeks. Only the cryoablation complete response rate increase from baseline was statistically significant.
Opioid Reduction Outcome	Reduction in opioids with respect to baseline was only significant for the cryo group (P=0.0039)
QOL Improvement Outcome	Both cryoablation and RFA showed statistically improvement QOL (p<0.001)
Approach & Protocol	15 Minute Freeze > 10 Minute Thaw > 15 Minute Freeze RFA: 10 W every 3 min up to 90 W, until tissue impedance increased and further current flow was prevented

Zugaro L, et al., Oncol Letters 2016; 11(3): 1948-1954

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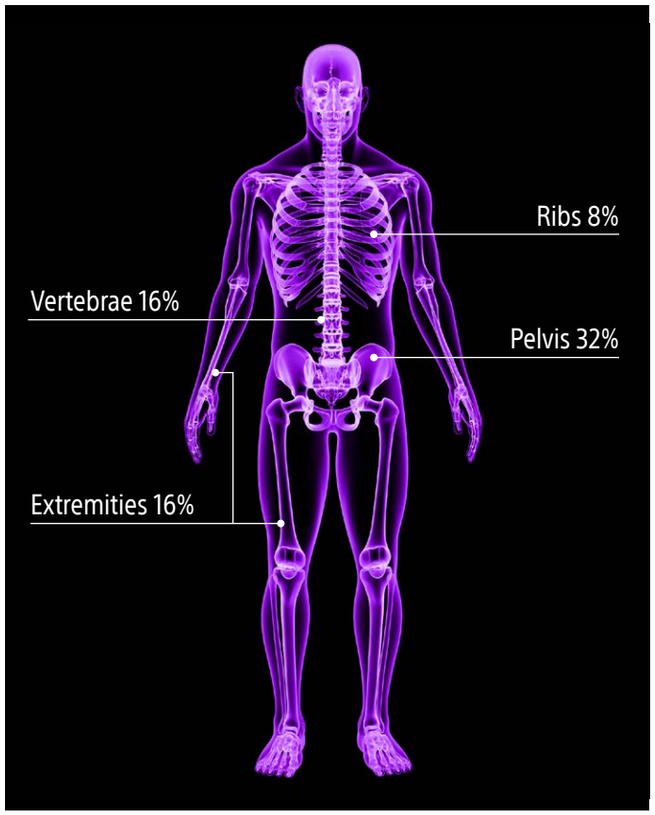
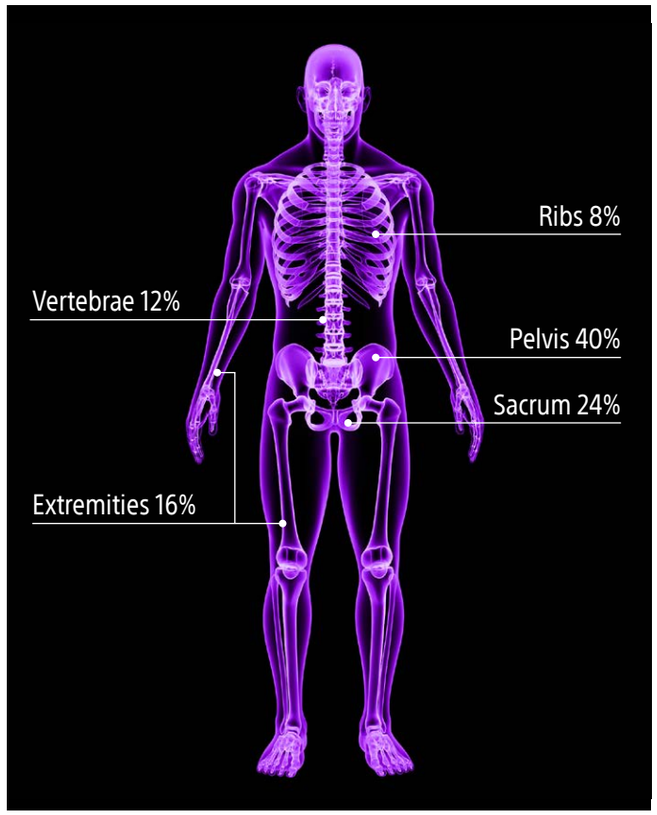
PAIN PALLIATION I CRYOABLATION vs. RFA

Zugago L, et al., 2016 I Index Tumor Locations

Cryoablation (n=25)



RFA (n=25)



Zugaro L, et al., Oncol Letters 2016; 11(3): 1948-1954

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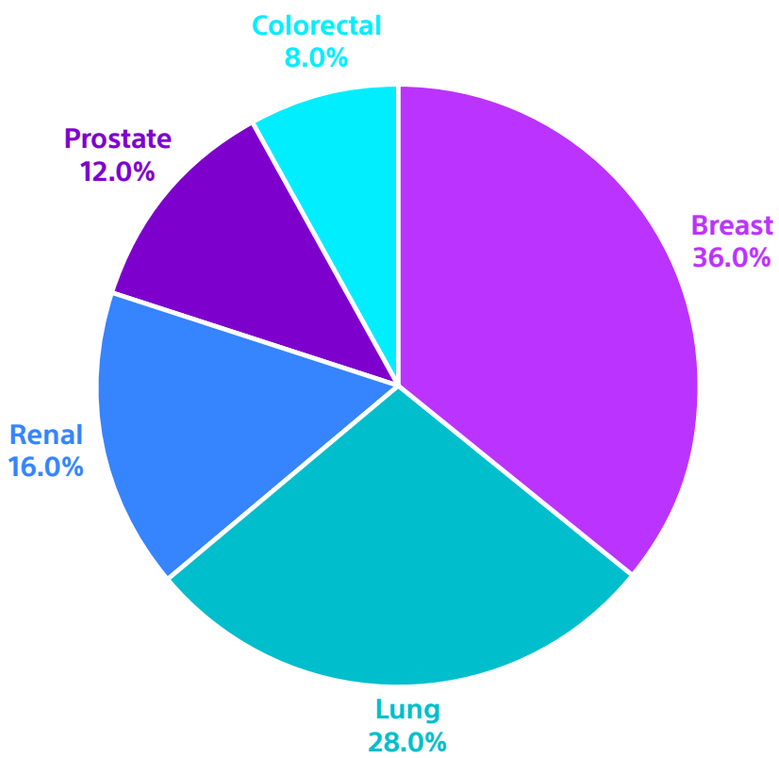
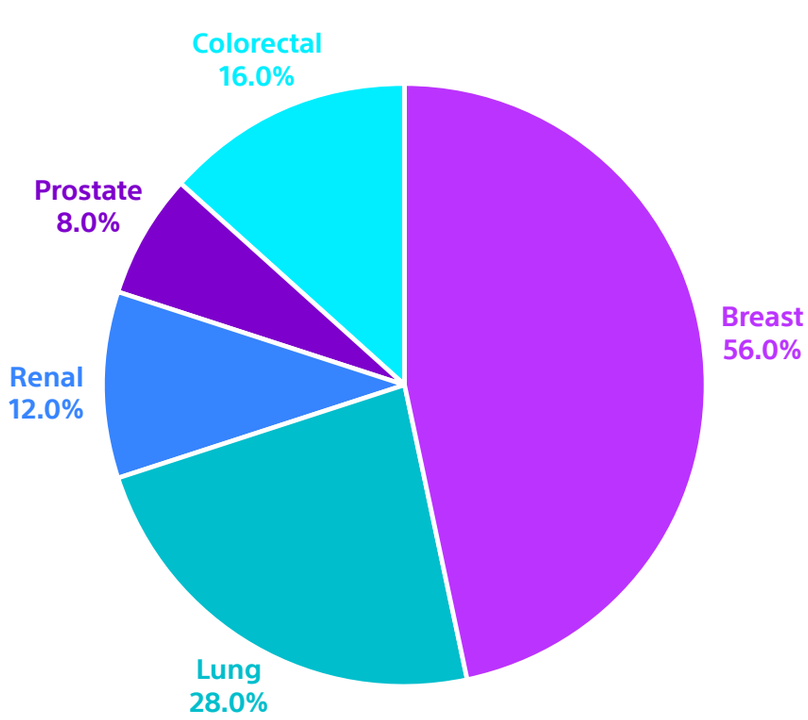
PAIN PALLIATION I CRYOABLATION vs. RADIATION

Zugago L, et al., 2016 I Tumor Type

Cryoablation (n=25)



RFA (n=25)



Zugaro L, et al., Oncol Letters 2016; 11(3): 1948-1954

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PAIN PALLIATION I CRYOABLATION vs. RADIATION

KEY STUDIES		VERTREBRAL			LARGE PELVIC	vs. RFA		vs. RADIATION
MOTION Study	Callstrom 2013	Tomasian 2016	Masala 2013	Cazzato 2022	Coupal 2017	Thacker PG 2011	**Zugago L 2016**	Di Staso M 2015

Zugago L, et al., 2016 I Pain Palliation and Safety

Pain Palliation:

- A higher proportion of subjects treated by cryoablation (32%) than RFA (20%) experienced a complete response at 12 weeks
- Only the cryoablation complete response rate increase from baseline was statistically significant

Safety:

- One complication from cryo (4%, 1/25, transient nerve injury) and one complication from RFA (4%, 1/25, transient nerve injury)

Zugaro L, et al., Oncol Letters 2016; 11(3): 1948-1954

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PAIN PALLIATION I CRYOABLATION vs. RADIATION THERAPY

Di Staso M, et al., 2015 I Treatment of Solitary Painful Osseous Metastases with Radiotherapy, Cryoablation or Combined Therapy: Propensity Matching Analysis in 175 Patients

Title	Treatment of Solitary Painful Osseous Metastases with Radiotherapy, Cryoablation or Combined Therapy: Propensity Matching Analysis in 175 Patients
Type of Study	Single center, retrospective, multi-arm, phase II study
Number of patients	175: 125 RT, 25 cryoablation, 25 patients RT + Cryo
Pain Reduction Outcome	A higher proportion of subjects treated by cryoablation (32%; p=0.018) or cryoablation followed by RT (72%; p<0.0001) experienced a complete response compared with patients treated by radiotherapy alone (11.2%)
Opioid Reduction Outcome	Significantly more patients were opioid-free at 12 weeks after cryo (n=9, 36%; p=0.0016) and cryo + RT (n=19, 76%; p<0.0001) compared to RT alone (17; 13.6%)
QOL Improvement Outcome	Both cryoablation alone and cryo + RT showed statistically increased quality of life improvements compared to TR alone (p=0.0018 and p=0.003; respectively)
Approach & Protocol	15 Minute Freeze > 10 Minute Thaw > 15 Minute Freeze RT was delivered by three-dimensional conformal technique with a dose of 20 Gy in five fractions of 4 Gy over 1 week

Di Staso M, et al., PLOS ONE 2015; 10(6): e0129021

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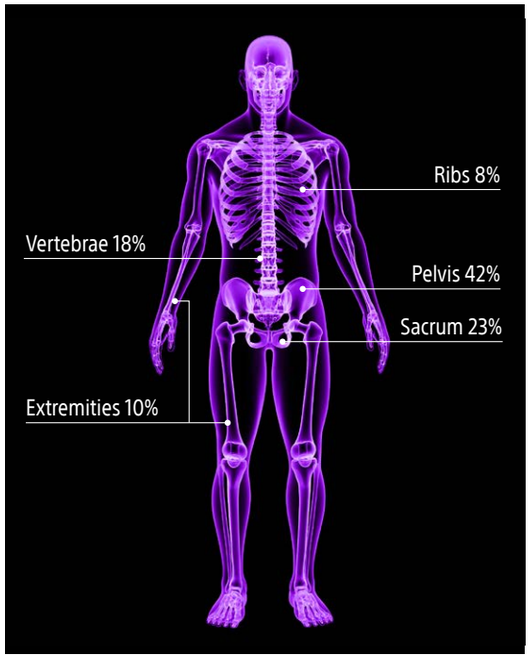
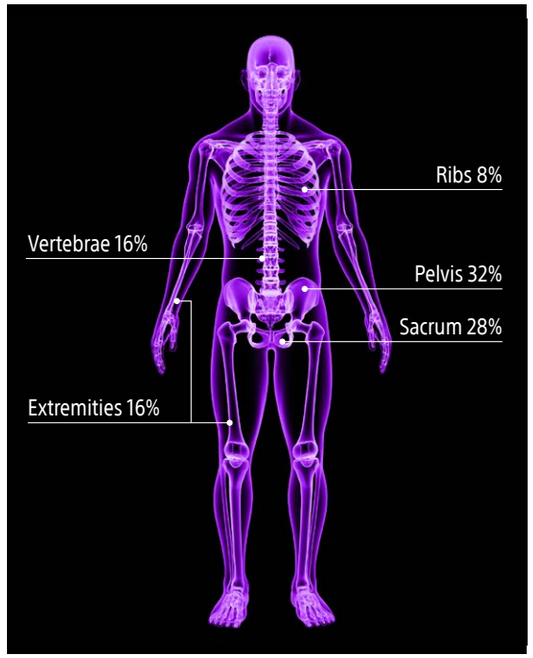
PAIN PALLIATION I CRYOABLATION vs. RADIATION

Di Staso M, et al., 2015 I Index Tumor Locations

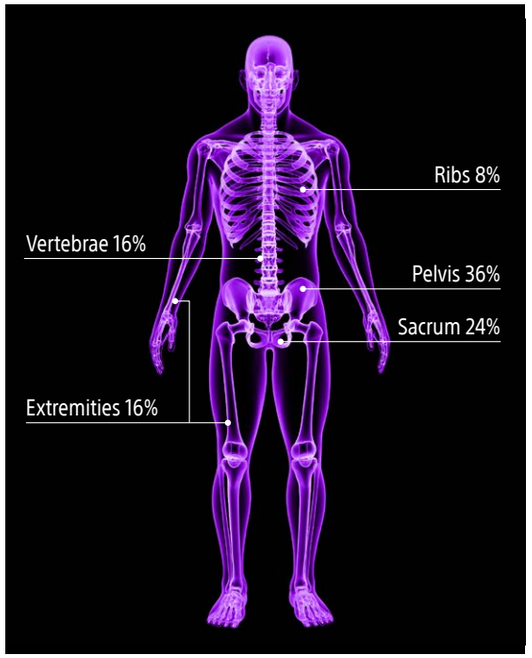
Radiation Therapy (n=125)



Cryoablation (n=25)



RT+Cryoabation (n=25)



Di Staso M, et al., PLOS ONE 2015; 10(6): e0129021

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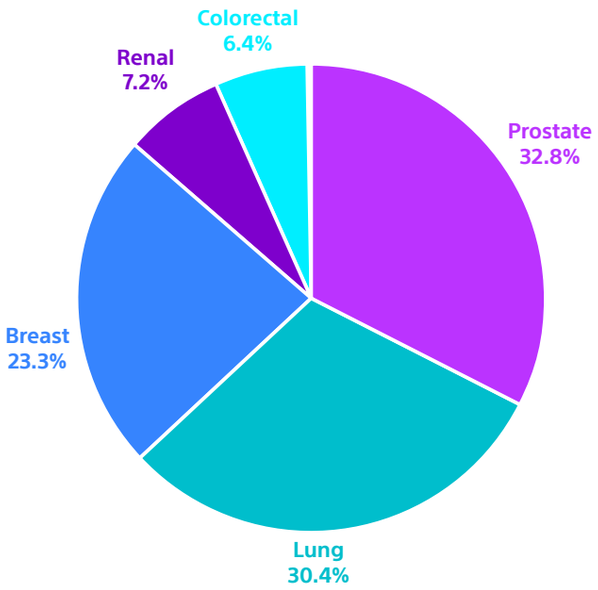
PAIN PALLIATION I CRYOABLATION vs. RADIATION

KEY STUDIES | VERTREBRAL | LARGE PELVIC | vs. RFA | vs. RADIATION

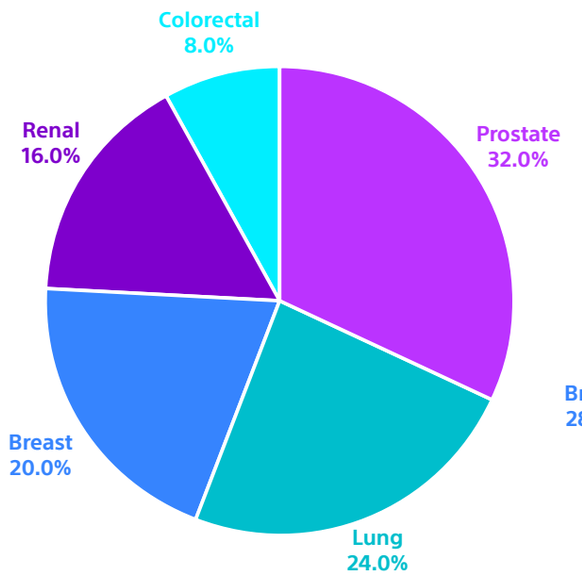
MOTION Study | Callstrom 2013 | Tomasian 2016 | Masala 2013 | Cazzato 2022 | Coupal 2017 | Thacker PG 2011 | Zugago L 2016 | Di Staso M 2015

Di Staso M, et al., 2015 I Tumor Type

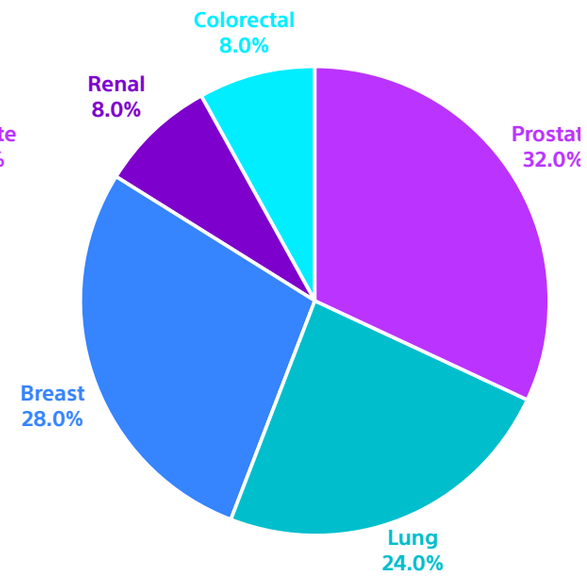
Radiation Therapy (n=125)



Cryoablation (n=25)



RT+Cryoabation (n=25)



Di Staso M, et al., PLOS ONE 2015; 10(6): e0129021

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PAIN PALLIATION I CRYOABLATION vs. RADIATION

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Di Staso M, et al., 2015 I Pain Palliation and Safety

Pain Palliation:

- A higher proportion of subjects treated by cryoablation (32%; p=0.018) or cryoablation followed by RT (72%; p<0.0001) experienced a complete response compared with patients treated by radiotherapy alone (11.2%)

Safety:

- Ten complications (20%, 10/50), gluteal, perineal, and thigh weakness (7/50), transient peripheral nerve injury (2/50), humerus fracture (1/50). RT complications were not reported.

Di Staso M, et al., PLOS ONE 2015; 10(6): e0129021

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PAIN PALLIATION | LOCAL CONTROL

Cryoablation Demonstrates Local Tumor Control

Patient Population

- Patients with limited metastatic burden/oligo metastatic disease (≤5 metastatic lesions)
  - All lesions are amenable for complete local treatment

Goal

- Produce an ablation zone that completely encompassed the gross tumor volume plus an ablative margin of 5–10 mm
- Local tumor control defined as no radiographic evidence of active tumor based on the following criteria: 1) no new or residual nodular or mass-like enhancement in the ablation bed, and 2) lack of hypermetabolism in the ablation bed on PET/CT.

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PAIN PALLIATION | LOCAL CONTROL

Spine Cryoablation

- Demonstrated local control through 12 months post cryoablation
  - 90% (37/41) @ 3 months
  - 86% (32/37) @ 6 months
  - 79% (26/33) @ 12 months

Wallace AN, et al., JVIR 2016; 27:1788–1796

- Demonstrated local control post cryoablation
  - 96.7% (30/31) @ median of 10 months

Tomasian A, et al., Am J Neuroradiol 2016; 37:189–195

- Demonstrated local control through 22 months post cryoablation
  - 82.1% (23/28) LTC @ mean of 25.9 ± 21.2 months

Cazzato RL, et al., Eur Radiol 2022; 32:4137–4146

Appendicular and Axial Cryoablation

- Demonstrated local control through 22 months post cryoablation
  - 90.9% (10/11) @ 22.4 months

Arrigoni F, et al., La Radiol Med 2022; 127:199–205

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OPIOID UTILIZATION I INTRODUCTION

Decreased Opioid Use Post Cryoablation

- Opioid use is a national epidemic with high rates of morbidity and mortality
- Opioid related deaths in cancer patients increased[18,19]
- Patients with painful bone metastases may have persistent pain that is refractory to opioids
- Decreased opioid utilization reduces opioid-related adverse event and improves the quality of life
- Several studies have shown that cryoablation decreases opioid utilization in patients with painful bone metastases

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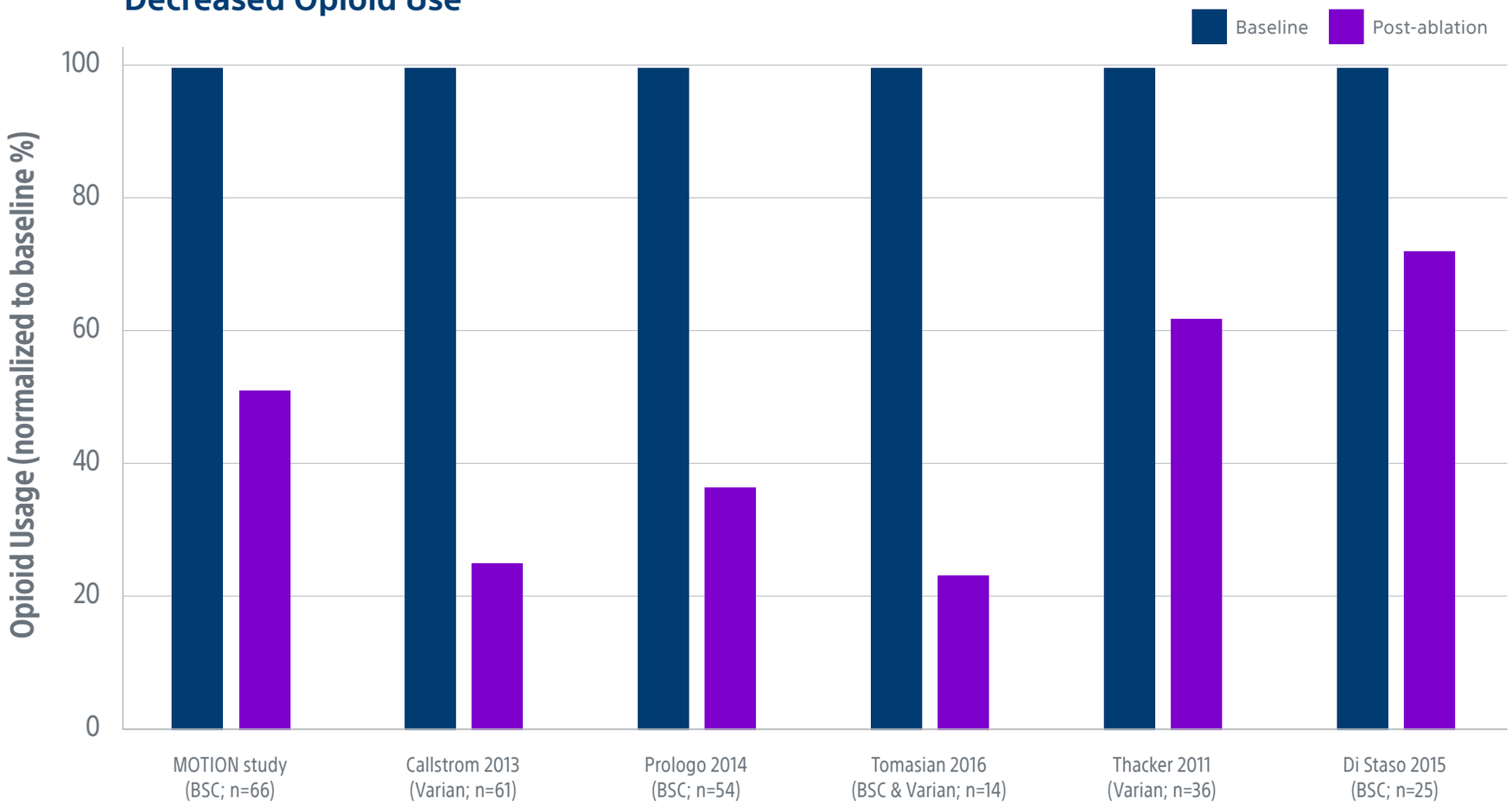
OPIOID UTILIZATION I OVERVIEW

Decreased Opioid Use



Decreased opioid utilization post-cryoablation data from 256 patients from six studies

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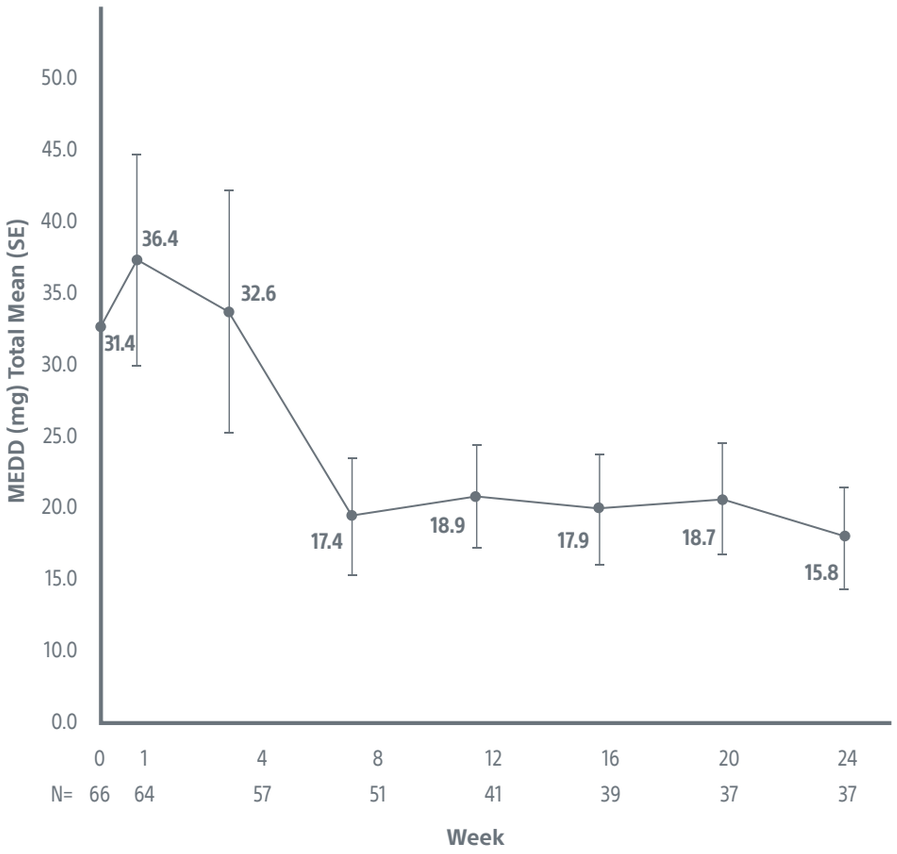
OPIOID UTILIZATION I MOTION STUDY

Mean Total Morphine Equivalent Daily Dose (MEDD)



- Opioid medication use at baseline
  - Reported by 48 of 66 (73%) participants
  - Mean MEDD of 43.1 mg ± 79.0 (median, 12.6 mg)
- Opioid medication use was reported by 56%–69% of participants who attended visits at week 4 through week 24
- MEDD among complete-case participants decreased from week 4 to week 24
- 57% (21 of 37) of participants with stable opioid pain medication (i.e., increased ≤ 25% over baseline) over week 4 through week 24

Jennings J, et al., Radiology: Imaging Cancer 2021; 3(2):e2001011

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OPIOID UTILIZATION | Callstrom MR, et al 2013

Opioid Utilization through 24 Weeks

	Baseline (N=61)	Week 1 (N=57)	Week 4 (N=49)	Week 8 (N=35)	Week 24 (N=16)
	Morphine-equivalent 24 hour dose (mg)				
Dose	113	76	96	130	29
P		.6526	.2138	.6365	.7952

Secondary endpoint:

- Percentage of patients who were able to reduce analgesic medications following treatment baseline to week 8.
  - 39 of 47 (83%, exact 95% confidence interval of 69 to 92%) reported a reduction in the use of opioid analgesic medications
- 40% (19 of 47; 95% CI of 26% to 56%) reported no opioid analgesic medications at some time following the cryoablation procedure

Jennings J, et al., Radiology: Imaging Cancer 2021; 3(2):e2001011

OPIOID UTILIZATION

Location and Cryo vs RFA and Radiation Therapy

Appendicular and Axial Cryoablation

- Narcotic use decreased from 340 ± 180 mg at baseline through 3 months
  - 85 ± 70 mg @ 1 day (p<0.000)
  - 130 ± 70 mg @ 3 months (p<0.000)

Prologo JD, et al., Skel Radiol 2014; 43:1551–1559

Spine Cryoablation

- Narcotic use decreased from 360 ± 105 mg at baseline through 3 months
  - 95 ± 55 mg @ 1 week (p<0.001)
  - 85 ± 50 mg @ 1 month (p<0.001)
  - 80 ± 45 mg @ 3 months (p<0.000)

Tomasian A, et al., Am J Neuroradiol 2016; 37:189–195

Cryoablation vs. RFA

- Analgesic use 24 hrs pre and post procedure was significantly lower with cryoablation (median –23.6 ± 137.0 MEQD; p=0.03) compared with RFA (median 21.6 ± 124.7 MEQD)

Thacker PG, et al., AJR 2011; 197: 510-515

- At 12 weeks, 20% of patients (5/25) in the RFA group and 36% of patients (9/25) in the cryo group did not require narcotic medication. Reduction in opioids with respect to baseline was only significant for the cryoablation group (P=0.0039)

Zugaro L, et al., Oncol Letters 2016; 11(3): 1948-1954

Cryoablation vs. Radiation Therapy

- Significantly more patients were opioid-free at 12 weeks after cryoablation (n=9, 36%; p=0.0016) and cryo + RT (n=19, 76%; p<0.0001) compared to RT alone (17; 13.6%)

Di Staso M, et al., PLOS ONE 2015; 10(6): e0129021

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QUALITY OF LIFE I INTRODUCTION

Cryoablation Increase Quality of Life

- Patients with painful bone metastases suffer from poor quality of life due to significant pain
- Additionally, these patients may have pathological fractures, incontinence, limb weakness, or symptoms associated with hypercalcemia, such as nausea, constipation and confusion which decrease their quality of life
- Treatments for painful bone metastases have specific side effects which also diminish quality of life
- Cryoablation has shown to increase the quality of life without the side effects of other treatments

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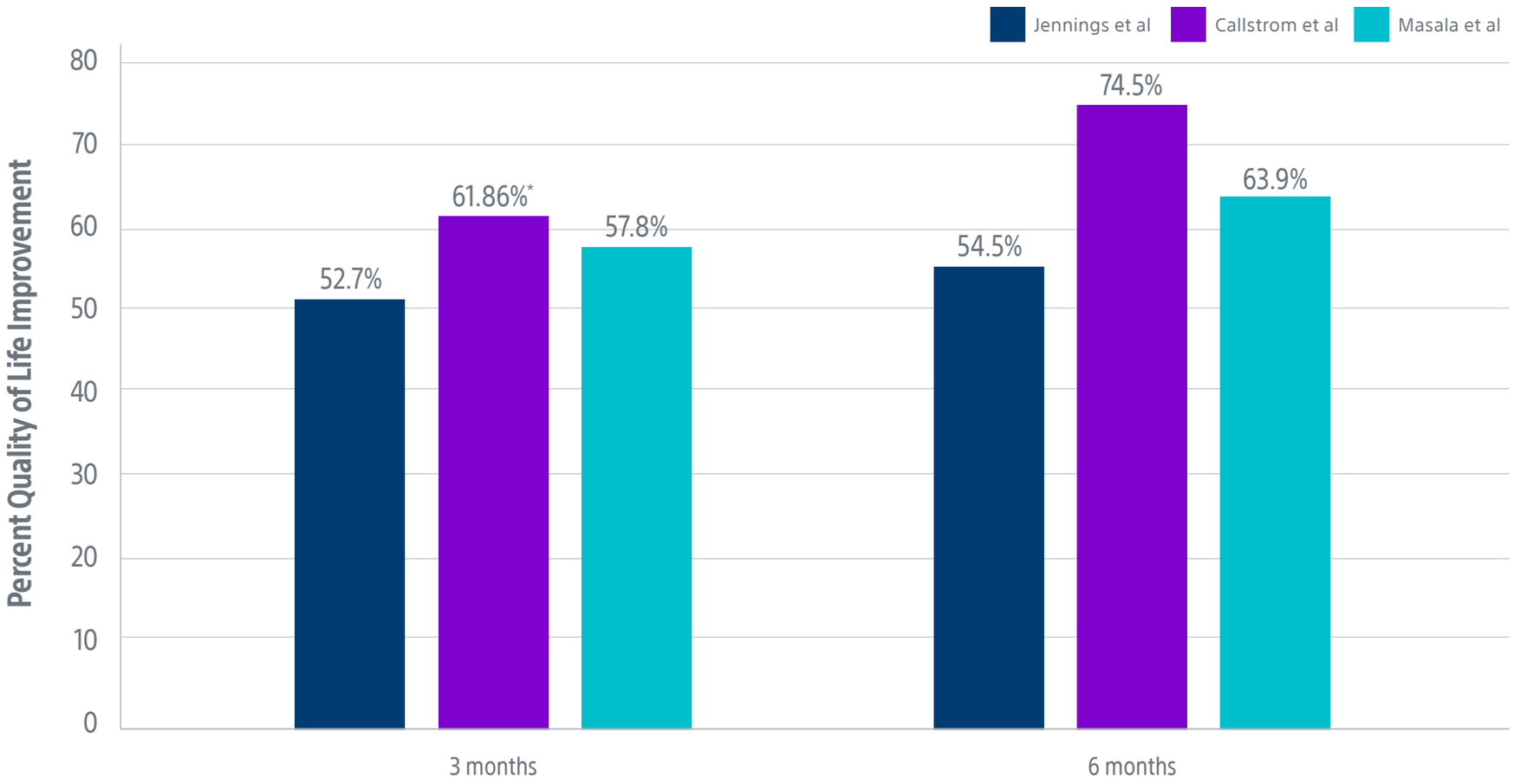
QUALITY OF LIFE | OVERVIEW

Improved Quality of Life Post Cryoablation at 3 and 6 months



* 8 weeks was closest reported timepoint to 12 weeks

Jennings J, et al., Radiology: Imaging Cancer 2021; 3(2):e200101
Callstrom MR, et al., Cancer 2013 Mar 1;119(5):1033-41.
Masala S, et al., Neuroradiology 2013; 55:193–200

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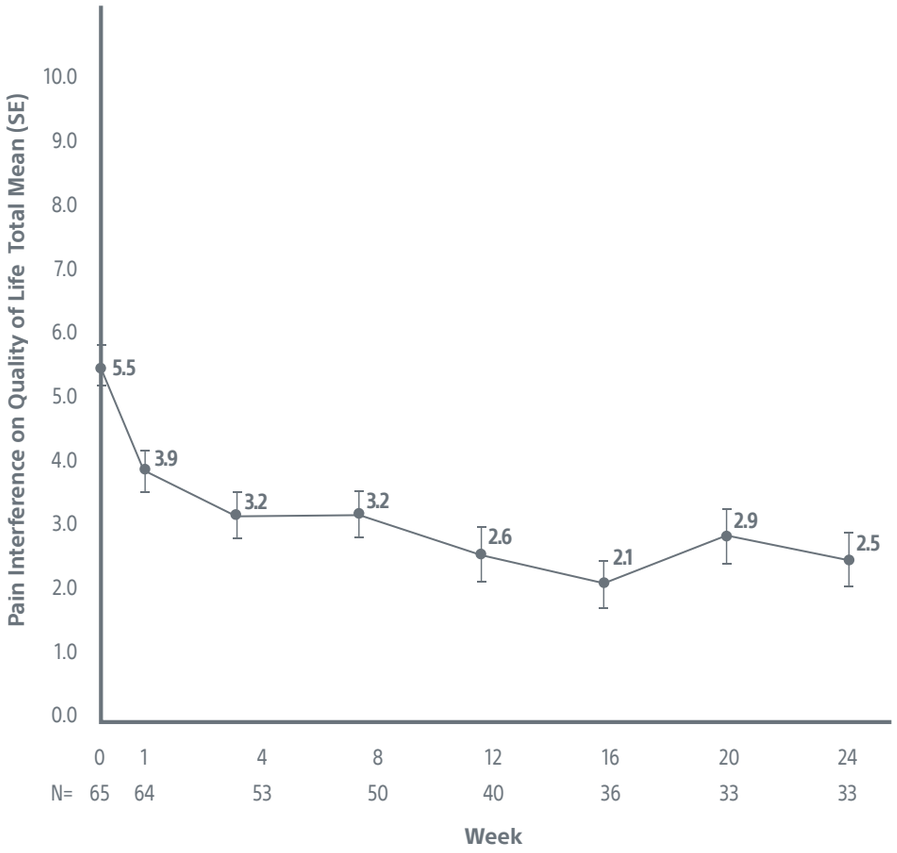
QUALITY OF LIFE I ASSESSMENT

Improved Quality of Life in MOTION Study



- **Quality of life consistently improved over 6 months**
- Treatment effect was rated “better than at the last visit” by:
  - 60.9% (39 of 64) at Week 1
  - 30% (11 of 37) Week 24
- Treatment effect was rated “worse than at the last visit” by:
  - 13% (8 of 64) at Week 1
  - 11% (4 of 37) Week 24

Jennings J, et al., Radiology: Imaging Cancer 2021; 3(2):e200101

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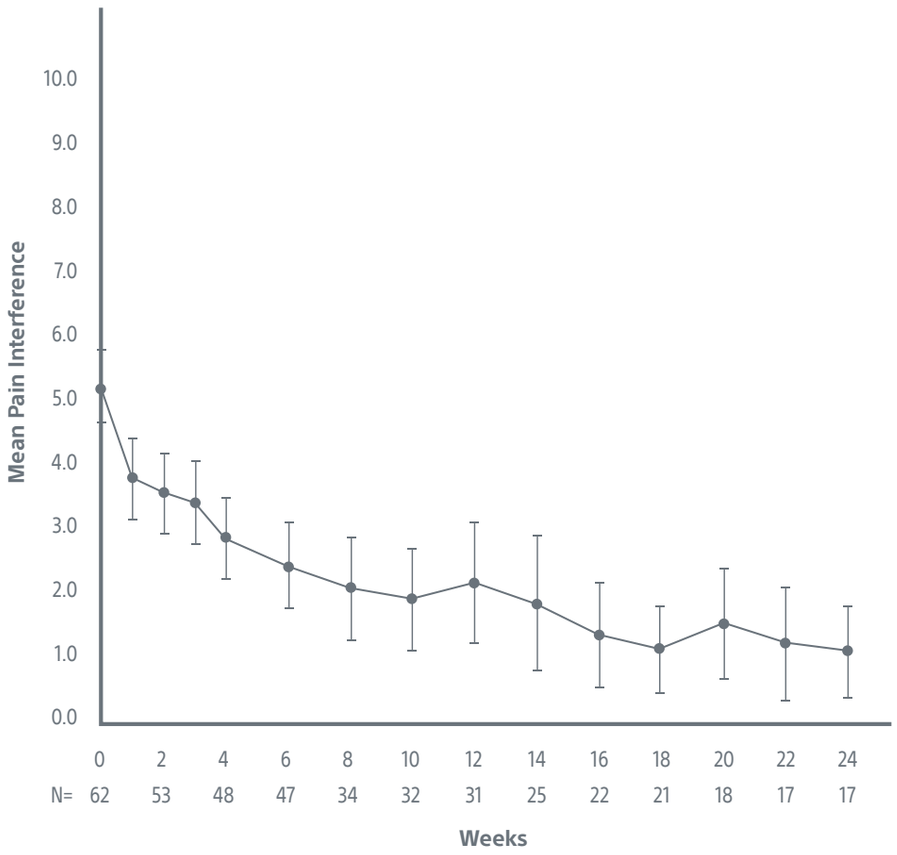
QUALITY OF LIFE | ASSESSMENT

Decreased Pain Interference Post Cryoablation



Quality of Life

- 67% (41/61) of patients over the course of the follow-up period experienced at least a 2-point reduction in mean score for interference of pain on activities of daily living

	Baseline (N=61)	Week 1 (N=57)	Week 4 (N=49)	Week 8 (N=35)	Week 24 (N=16)
	Pain interference (0-10)				
Dose	5.2	3.8	2.9	2.1	1.1
P		.0004	<.0001	<.0001	<.0001

Callstrom MR, et al., Cancer 2013 Mar 1;119(5):1033-41

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QUALITY OF LIFE I ASSESSMENT

Improved Quality of Life with Cryoablation + Vertebroplasty

Oswestry Disability Index (ODI)* score showed a statistically significant difference between patients treated with CVT and patients managed with VT (p<0.001)

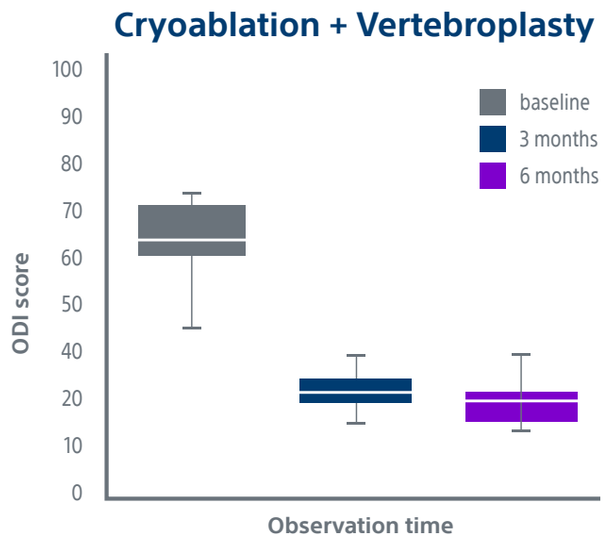
- 3 months (25.6 ± 4.35 vs. 45.2 ± 6.62), (p<0.001)
- 6 months (26.55 ± 4.12 vs. 40.65 ± 7.19), (p<0.001)

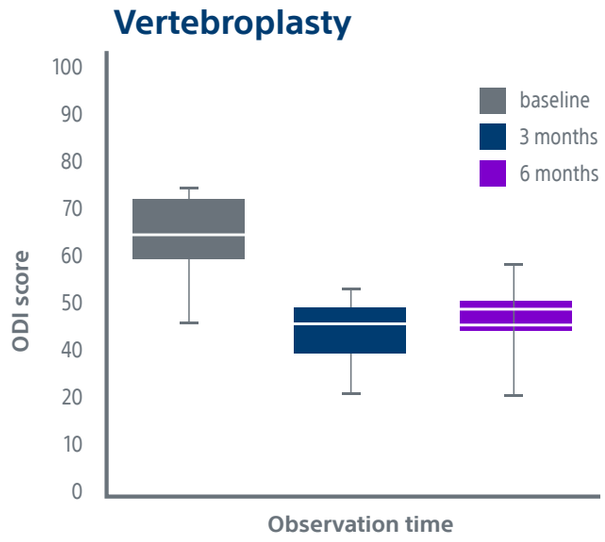
CVT

- QOL improved from 60.65% ± 8.36 ODI at baseline through 6 months
  - 25.60% ± 4.35 @ 3 month (p<0.0001)
  - 22.43% ± 4.12 @ 6 months (p<0.0001)

CVT

- QOL improved from 59.52% ± 9.50 ODI at baseline through 6 months
  - 38.56% ± 6.62 @ 3 month (p<0.0001)
  - 40.65% ± 7.19 @ 6 months (p<0.0001)





*The ODI is scored on a scale of 0-100, with a score of 0-20 reflecting minimal disability, 21-40 moderate disability, 41-60 severe disability, 61-80 crippled, and 81-100 bed-bound

Masala S, et al., Neuroradiology 2013; 55:193–200

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QUALITY OF LIFE I ASSESSMENT

Improved Quality of Life with Cryoablation

Cryoablation vs. RFA

- Total hospital length of stay for patients undergoing cryoablation was a median of 2.5 days less than that for patients receiving RFA (p = 0.003)

Thacker PG, et al., AJR 2011; 197: 510-515

- Both cryoablation and RFA showed statistically improvement quality of life (p<0.001)

Zugaro L, et al., Oncol Letters 2016; 11(3): 1948-1954

Cryo vs. Radiation Therapy

- Both cryoablation alone and cryo + RT showed statistically increased quality of life improvements compared to TR alone (p=0.0018 and p=0.003; respectively)

Di Staso M, et al., PLOS ONE 2015; 10(6): e0129021

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KEY TECHNIQUES I PROTECTION OF CRITICAL STRUCTURES

Displacement Techniques: Hydro- and Pneumo- and Balloon Dissection

- Critical structures may be protected by displacing using hydro/pneumo-dissection or balloons
- Hydrodissection
  - A small needle is advanced between the tumor and the critical structure
  - Sterile water or saline is typically used for displacement
  - Intermittent scanning to confirm appropriate displacement through freeze-thaw protocol
- Pneumo-dissection
  - A small needle is advanced between the tumor and the critical structure
  - Utilization of gases for pneumo-dissection is useful as it displaces the critical structure (e.g. skin), as well as provides an insulative buffer between the sensitive structure and ice ball
  - Carbon dioxide has become the gas of choice as it is readily available, decreased infection rate relative to air, and lower thermal conductivity than air.
  - CO^2 also has increased absorption compared to air, thus decreasing the potential for embolism
- Balloon dissection
  - Angioplasty, endoscopic, and vertebral augmentation balloons have been used for displacement of critical structures

Warming Techniques – Skin Protection

- Warmed bag of saline or sterile glove with warm saline or water
- Gauze soaked with warm sterile saline
- Hand of the interventionalist
- Heat lamps

Kurup AN, et al., Cardiovasc Intervent Radiol 2017; 40: 166-176

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KEY TECHNIQUES I TEMPERATURE & NEURAL MONITORING

Visualization

- Leading edge of ice ball on CT is 0°C and thus helpful to visualize when close to temperature sensitive structures
- Intraprocedural monitoring of ice ball development is the most employed method used to identify proximity of ice ball to targeted lesion and critical structures

Temperature

- Using temperature probes has been employed to prevent neural injury which can occur at ≤ 10°C

Neural

- Neurophysiologic monitoring has proven to have high sensitivity to detect post-procedural motor deficits
  - Motor evoked potentials
  - Somatosensory evoked potentials

Kurup AN, et al., Cardiovasc Intervent Radiol 2017; 40: 166-176

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KEY TECHNIQUES I AUGMENTATION AND FIXATION

Reducing Bone Fracture

- Augmentation using cementoplasty after cryoablation of bone metastases has become an essential component for osteolytic lesions
- Cement provides additional strength to protect against compressive forces in weight-bearing bones
- However, it is less effective against shear or torsional forces commonly exerted on pelvic and long bones
- Therefore, these bones often require further fixation with rods and nails
- Cement should be slowly injected to prevent leakage and sufficient time post-cryoablation to allow for thawing (15-30 min or next day)

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KEY TECHNIQUES I RISKS AND MITIGATIONS

Cryoablation of Painful Bone Metastases

Important Risks	Mitigations
Fracture (especially for weight-bearing bones)	• Vertebral augmentation • Cementoplasty • Fixation with screws or nails
Neural structures (especially motor neurons) **• Spinal cord** **• Sacral nerve roots** **• Sciatic nerve** **• Femoral nerve** **• Brachial plexus**	• Pre-procedure MRI • CT angiography • Motor or somatosensory evoked potentials • Electrostimulation • Pre-ablation myelography • Steroids • NSAIDs • Anti-neuropathics (e.g. gabapentin) • Temperature sensors
Skin	• Warm saline on surface of skin • Subdermal pneumo-dissection • Subdermal hydro-dissection • Temperature sensors
Osteochondral Injury	• Place needles to avoid freezing femoral head and hip joint
Gas embolization from damaged needle	• Always test the full length of needle • Visualize placed needles prior to placing subsequent needles, including biopsy needles

Kurup AN, et al., Cardiovasc Intervent Radiol 2017; 40: 166-176

ENDNOTES

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