

Evidence-to-Decision table 6.2		
In adults (including older persons) and adolescents with pain related to bone metastases, is radiotherapy more effective than no radiotherapy for achieving pain control?		
<b>POPULATION:</b>	Adults (including older persons) and adolescents with cancer-related pain	<p><b>Background:</b></p> <p>Bone pain is the most common type of pain from cancer and is present in approximately one out of three patients with bone metastases.<sup>129,139</sup> The pain is commonly a mixture of background pain and incident/episodic pain, which is commonly associated with weight bearing or movement.<sup>130</sup> Bone metastases can weaken bone sufficiently to greatly increase patients' risk of fracture.</p> <p>Radioisotopes can be administered for diffuse bone pain that is ineligible for radiotherapy.</p> <p><b>Current WHO recommendation:</b> None</p>
<b>INTERVENTION:</b>	Radioisotopes or radiotherapy	
<b>COMPARISON:</b>	Placebo (no treatment)	
<b>MAIN OUTCOMES:</b>	<ul style="list-style-type: none"> <li>• Bone pain relief</li> <li>• Pain relief maintenance</li> <li>• Quality of life (QoL)</li> <li>• Functional outcomes</li> <li>• Skeletal-related events</li> <li>• Bone pain (adverse event)</li> </ul>	
<b>STRATIFICATIONS:</b>	<ul style="list-style-type: none"> <li>• Age (adults, older persons, adolescents, children)</li> <li>• History of substance abuse</li> <li>• Refractory pain</li> </ul>	
<b>SETTING:</b>	All	
<b>PERSPECTIVE:</b>	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
<b>PROBLEM</b>	<p><b>Is the problem a priority?</b> None</p>	<p><b><u>Research evidence</u></b> None</p> <p><b><u>Additional considerations</u></b> Due to the high cost of treatment worldwide calling into question the global relevancy of the therapy, as well as the homogeneity of evidence, the GDG did not feel confident issuing a recommendation.</p>

Do the desirable effects outweigh the undesirable effects?

Yes  No  Uncertain

- **Nine randomized controlled trials** compared radioisotopes to a control with no radioisotopes in patients almost all with prostate cancer. The studies evaluated strontium-89 (3 trials), samarium-153 (3 trials), rhenium-186 (2 trials), and radium-223 (1 trial). Trials were mostly conducted in older adults.

#### BENEFITS and HARMS

- **Five trials** provided **moderate strength of evidence** of **better bone pain relief with radioisotope treatment**. The net difference in bone pain was -41 points (on a 0 to 100 [worst] scale; 95% CI -64, -18), favouring radioisotopes. **Two and four trials**, respectively, provided **very low strength of evidence** that **bone pain relief** was **more common after radioisotopes** (38%) versus placebo (20%, RR = 1.92; 95% CI 1.18, 3.12) and that **bone pain improvement** was **more common after radioisotopes** (66%) versus placebo (43%, RR = 1.35; 95% CI 0.89, 2.07) .
- **No trial** reported on **pain relief speed**.
- **No trial** reported on **pain relief maintenance**.
- **Two trials** provided **high strength of evidence** that **skeletal related events (any) were less common after radioisotopes than placebo** (RR = 0.86; 95% CI 0.77, 0.95) and that **skeletal related events were delayed among those who had received radioisotopes compared to placebo** (HR = 0.73; 95% CI 0.62, 0.86).
- **Two trials** provided **low strength of evidence** of **similar risk of fracture** (RR = 1.05; 95% CI 0.53, 2.08)
- **Two trials** provided **low strength of evidence** of **similar risk of spinal cord compression** (RR = 0.82; 95% CI 0.39, 1.71).
- **One trial** provided **very low strength of evidence** for **bone surgery** (RR = 1.46; 95% CI 0.69, 3.10).
- **One trial** provided **very low strength of evidence** for **hypercalcemia** (RR = 5.01, 95% CI 0.24, 104).
- **Two trials** provided **moderate strength of evidence** that **QoL was probably improved more with radioisotopes than placebo** when measured continuously (difference = 1.5; 95% CI -0.4, 3.3 on a transformed 0 to 100 [best] scale). **One trial** provided **low strength of evidence** that **QoL may be improved more with radioisotopes than placebo** when measured categorically (RR = 1.57; 95% CI 1.17, 2.10).
- **One trial** provided **very low strength of evidence** regarding **functional outcomes (social or physical) with radioisotopes or placebo**: social function favoring placebo (between-group difference -1.1; 95% CI -1.9, -0.3), physical function favoring radioisotopes (between arm difference 1.4; 95% CI 0.5, 2.3); both not statistically significant per trial authors.
- **Three trials** provided **low strength of evidence** of **no difference in episodes of acute bone flares with radioisotopes** (6.8%, RR = 1.30; 95% CI 0.50, 3.42) than placebo (4.9%).

#### STRATIFICATIONS

- Studies conducted in mostly older adults with a mostly narrow age range, without stratification into adolescent, non-older persons, and older persons.
- Studies provide no data regarding history of substance abuse.

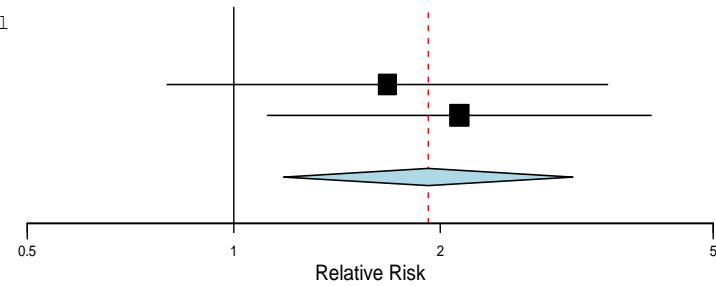
- Studies provide no data regarding refractory pain.

**SUMMARY**

Radioisotope treatment reduces and delays skeletal related events, probably reduces bone pain and improves QoL.

**Forest Plot 6.2.1. Pain Relief (“Complete Response”, Categorical) Radioisotope Versus Placebo**

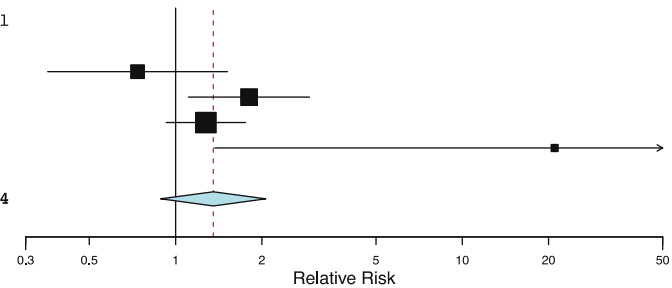
Studies	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
Porter 1993	1.674 (0.800, 3.506)	13/33	8/34
Sartor 2004	2.132 (1.120, 4.059)	38/101	9/51
<b>Overall (I<sup>2</sup>=0 %, P=0.629)</b>	<b>1.921 (1.182, 3.121)</b>	<b>51/134</b>	<b>17/85</b>



**Abbreviations:** *CI:* confidence interval; *Ctrl:* control (radioisotope); *Ev:* events (pain relief); *Trt:* treatment (placebo).

**Forest Plot 6.2.2. Pain Improvement (“Complete or Partial Response”, Categorical) Radioisotope Versus Placebo**

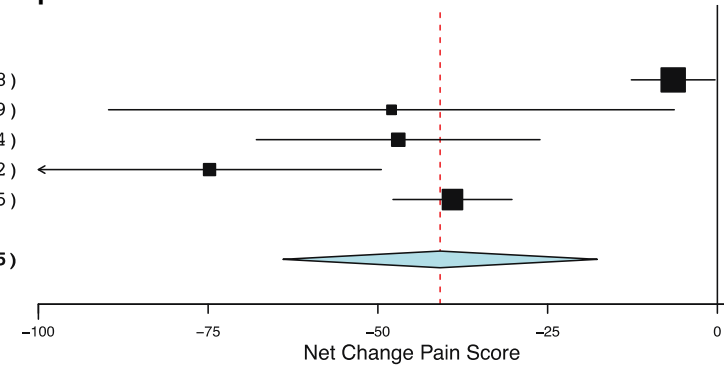
Studies	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
Buchali 1988	0.737 (0.358, 1.517)	7/19	11/22
Han 2002	1.803 (1.109, 2.933)	28/43	13/36
Porter 1993	1.276 (0.928, 1.754)	26/33	21/34
Storto 2013	21.000 (1.368, 322.278)	10/12	0/12
<b>Overall (I<sup>2</sup>=48%, P=0.045)</b>	<b>1.354 (0.887, 2.066)</b>	<b>71/107</b>	<b>45/104</b>



**Abbreviations:** *CI:* confidence interval; *Ctrl:* control (radioisotope); *Ev:* events (pain relief); *Trt:* treatment (placebo).

### Forest Plot 6.2.3. Pain Relief (Continuous) Radioisotope Versus Placebo

Studies	Estimate (95% CI)
Han 2002	-6.500 (-12.672, -0.328)
Maxon 1991	-48.000 (-89.661, -6.339)
Sartor 2004	-47.000 (-67.886, -26.114)
Serafini 1998	-74.785 (-100.068, -49.502)
Storto 2013	-39.000 (-47.765, -30.235)
<b>Overall (<math>I^2=93\%</math>, <math>P&lt;0.001</math>)</b>	<b>-40.826 (-63.976, -17.675)</b>

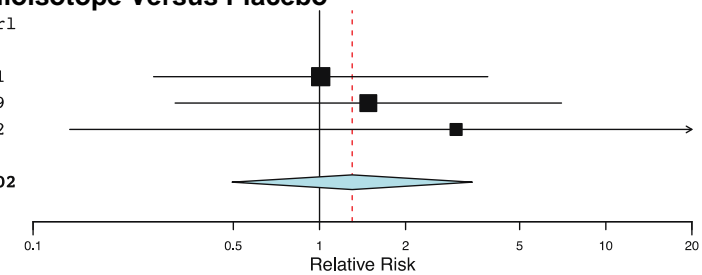


**Abbreviation:** *CI*: confidence interval.

Scores from individual studies have been transformed to a uniform 0-100 scale (100 = worst).

### Forest Plot 6.2.4. Bone Flares (Adverse Event) Radioisotope Versus Placebo

Studies	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
Sartor 2004	1.010 (0.263, 3.874)	6/101	3/51
Serafini 1998	1.481 (0.313, 7.003)	6/79	2/39
Storto 2013	3.000 (0.134, 67.056)	1/12	0/12
<b>Overall (<math>I^2=0\%</math>, <math>P=0.802</math>)</b>	<b>1.301 (0.495, 3.419)</b>	<b>13/192</b>	<b>5/102</b>



**Abbreviations:** *CI*: confidence interval; **Ctrl**: control (radioisotope); **Ev**: events (pain relief); **Trt**: treatment (placebo).

<b>ACCEPTABILITY &amp; PREFERENCES</b>	<p><b>Is there important uncertainty or variability about how much people value the options?</b></p> <p>Major variability <input type="checkbox"/></p> <p>Minor variability <input type="checkbox"/></p> <p>Uncertain <input type="checkbox" value="Yes"/></p> <p><b>Is the option acceptable to key stakeholders?</b></p> <p>Yes    No    Uncertain  <input type="checkbox"/>    <input type="checkbox"/>    <input type="checkbox" value="Yes"/></p>	<p><u>Research evidence</u> None</p> <p><u>Additional considerations</u> None</p>

<b>FEASIBILITY ./ RESOURCE USE</b>	<p><b>How large are the resource requirements?</b></p> <p>Major    Minor    Uncertain</p> <p><input type="checkbox"/>    <input type="checkbox"/>    <input type="checkbox"/> Yes</p>	<p><b><u>Research evidence</u></b></p> <p>None</p>
	<p><b>Is the option feasible to implement?</b></p> <p>Yes    No    Uncertain</p> <p><input type="checkbox"/>    <input type="checkbox"/>    <input type="checkbox"/> Yes</p>	<p><b><u>Additional considerations</u></b></p> <p>None</p>
	<p><b>Would the option improve equity in health?</b></p> <p>Yes    No    Uncertain</p> <p><input type="checkbox"/>    <input type="checkbox"/>    <input type="checkbox"/> Yes</p>	<p><b><u>Research evidence</u></b></p> <p>None</p> <p><b><u>Additional considerations</u></b></p> <p>None</p>

<b>Recommendation</b>	<b>Current recommendation:</b>
	None
	<b>New (draft) recommendation:</b>
	None
<b>Strength of Recommendation</b>	
<b>Quality of Evidence</b>	<p>➤ <b>LOW</b>  [Bone pain (critical) = very low (categorical), moderate (continuous)  Any SRE (important) = high  QoL (important) = low (categorical), moderate (continuous)  Acute bone flare (important) = low  other outcomes omitted for no data, conflicting, no difference, or indeterminate findings]</p>
<b>Justification</b>	Radioisotopes are not a priority for WHO to make guidance due to price and homogeneity of evidence.
<b>Subgroup considerations</b>	
<b>Implementation considerations</b> [incl. M&E]	
<b>Research priorities</b>	