

Evidence-to-Decision table 6.1

In adults (including older persons) and adolescents with pain related to bone metastases, is low-fractionated radiotherapy more effective than high-fractionated radiotherapy for achieving pain control?

POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	<p>Background:</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.^{129,139} The pain is commonly a mixture of background pain and incident/episodic pain, which is commonly associated with weight bearing or movement.¹³⁰ Bone metastases can weaken bone sufficiently to greatly increase patients' risk of fracture.</p> <p>Radiotherapy has been shown to reduce pain significantly and is reported to be the most effective treatment specific for cancer-related bone pain. Previous reviews have found no important differences between single dose radiotherapy and multiple dose therapy.^{190,191}</p> <p>Current WHO recommendation: None</p>
INTERVENTION:	Radiotherapy (low-fractionated)	
COMPARISON:	Radiotherapy (high-fractionated)	
MAIN OUTCOMES:	<ul style="list-style-type: none"> • Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Skeletal-related events • Acute bone flare (adverse event) 	
STRATIFICATIONS:	<ul style="list-style-type: none"> • Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain 	
SETTING:	All	
PERSPECTIVE:	Population	

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	<p>Is the problem a priority? Yes</p>	<p><u>Research evidence</u> None</p> <p><u>Additional considerations</u> Radiotherapy is a relatively expensive therapy limited only to settings with adequate capacity to deliver it. Nevertheless, it is a therapy offered in many countries, including low- and middle-income countries, with well-known therapeutic benefits. WHO guidance is therefore needed on which treatment schedule is preferred: low-fractionated/single dose radiotherapy or high-fractionated/multiple dose radiotherapy?</p>

Do the desirable effects outweigh the undesirable effects?

Yes	No	Uncertain
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		Yes

- **Twenty-three randomized controlled trials** compared low-fractionated (single dose) radiotherapy to high-fractionated (multiple dose) radiotherapy in patients with a variety of cancer types, with breast, prostate, and lung cancers seen in most studies. Almost all trials used an 8 Gy single dose in the low-fractionated arm; various schedules were used in the high-fractionation arms ranging from 20 to 30 Gy mostly given over 5 to 10 fractions. Among studies that reported participant ages, study participants were mostly older adults; the mean age ranged from 48 to 72 years old, with the youngest participant being 16 years old.

BENEFITS and HARMS

- **Eighteen trials** provided **high strength of evidence** that the **different fractionation schedules were similarly effective in producing complete pain relief** (“complete response”). Under both schedules, 25% or 26% of participants achieved complete pain relief (RR = 0.97; 95% CI 0.89, 1.06).
Twenty-one trials provided **high strength of evidence** that the **different fractionation schedules were similarly effective in improving pain relief** (“complete or partial response”). Under both schedules, 69% or 71% of participants achieved either complete or partial pain relief (RR = 0.97; 95% CI 0.93, 0.998).
Three trials provided **low strength** of evidence of no difference of pain relief (measured on a continuous scale) between fractionation schedules. The difference between groups in pain score on a transformed 0-100 (worst) scale ranged from -5 to 2.5 units.
- **Three trials** provided **moderate strength of evidence** of **similar pain relief speed** (time to pain relief) **with both schedules**. No significant differences were found.
- **Nine trials** provided **moderate strength of evidence** of **similar pain relief maintenance** (duration of pain relief) **with both schedules**. No significant differences were found.
- **Ten trials** provided **high strength of evidence** that rates of **pathological fractures (at the index site)** were **more likely with low-fractionated** compared with high-fractionated radiotherapy (RR = 1.48; 95% CI 1.08, 2.03).
- **Three trials** provided **high strength of evidence** that rates of **spinal compression (at the index site)** were **more likely with low-fractionated** compared with high-fractionated radiotherapy (RR = 1.45; 95% CI 0.89, 2.37).
- **Three trials** provided **low strength of evidence** of **no significant differences between fractionation schedules in improvements in QoL** (RR = 1.02; 95% CI 0.83, 1.26) measured using various scales.
- **Three trials** provided **low strength of evidence** of **no significant differences between fractionation schedules in improvements in physical function** (RR = 1.11; 95% CI 0.84, 1.46) measured using various scales, and **one trial** provided **very low strength of evidence** of **no significant difference between fractionation schedules in social function** (RR = 0.98; 95% CI 0.8, 1.20), as measured on the QLQ-C30 scale.
- **One trial** provided **low strength of evidence** of **more acute bone flares with low-fractionated** than high-fractionated radiotherapy (RR = 3.45; 95% CI 0.73, 16.3).

STRATIFICATIONS

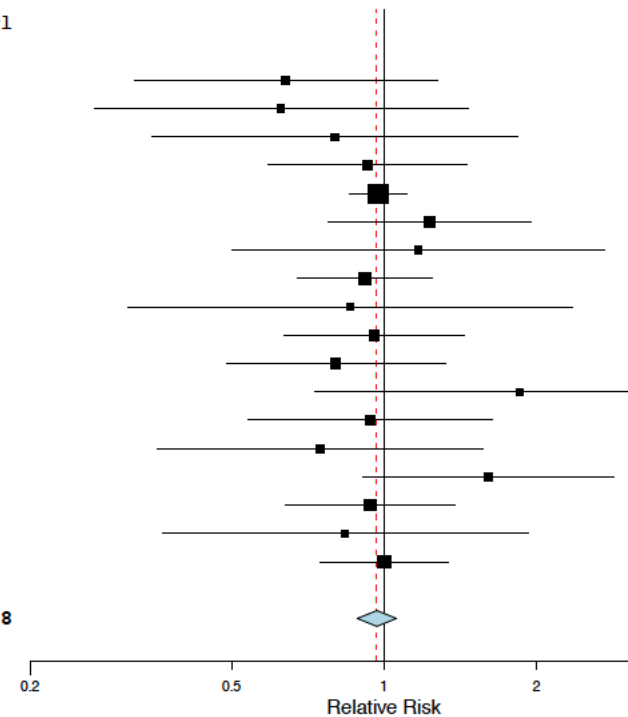
- Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons.
- Studies provide no data regarding history of substance abuse.
- Studies provide no data regarding refractory pain.

SUMMARY

The choice of low-fractionated (single dose) or high-fractionated (multiple dose) radiotherapy makes little or no difference in bone pain relief, but high-fractionated (multiple dose) radiotherapy reduces the risk of pathological fractures and spinal compression at the index sites. The choice of radiotherapy schedule probably makes little or no difference in speed or duration of pain relief and may make little or no difference in quality of life or function. Low-fractionated (single dose) radiotherapy may cause more acute bone flares than high-fractionated (multiple dose) radiotherapy.

Forest Plot 6.1.1. Pain Relief (“Complete Response”, Categorical) Single vs. Multiple Fractionated Radiotherapy

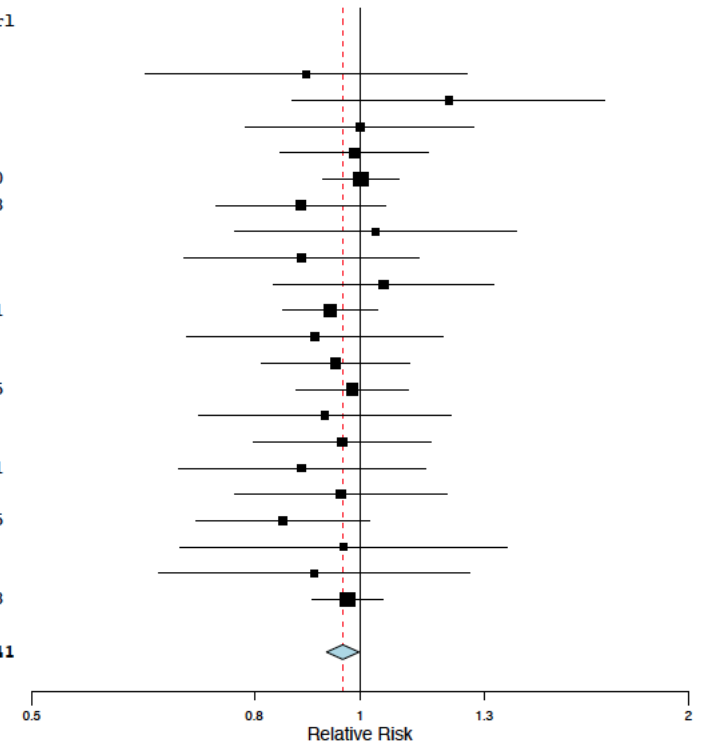
Studies	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
Altundag 2002	0.641 (0.321, 1.276)	7/17	9/14
AmouzegarHashemi 2008	0.626 (0.268, 1.466)	6/27	11/31
Anter 2015	0.800 (0.349, 1.836)	8/44	10/44
Badzio 2003	0.928 (0.590, 1.460)	23/64	24/62
BPTWP 1999	0.974 (0.856, 1.109)	199/351	192/330
Chow 2014	1.230 (0.776, 1.951)	35/258	29/263
Foro Arnalot 2008	1.168 (0.502, 2.721)	10/78	9/82
Gaze 1997	0.915 (0.673, 1.244)	50/129	47/111
Gutierrez Bayard 2014	0.857 (0.312, 2.351)	6/45	7/45
Hamouda 2007	0.957 (0.634, 1.445)	23/50	25/52
Hartsell 2005	0.803 (0.488, 1.321)	25/256	31/255
Kagei 1990	1.857 (0.730, 4.722)	8/14	4/13
Koswig 1999	0.940 (0.539, 1.640)	16/52	18/55
Nielsen 1998	0.749 (0.357, 1.571)	11/106	14/101
Price 1986	1.609 (0.908, 2.850)	22/49	12/43
Roos 2005	0.940 (0.637, 1.385)	35/119	36/115
Sarkar 2002	0.838 (0.365, 1.926)	6/17	8/19
van der Linden 2004	1.002 (0.748, 1.343)	78/556	76/543
Overall (I²=0%, P=0.897)	0.968 (0.886, 1.058)	568/2232	562/2178



Abbreviations: BPTWP: Bone Pain Trial Working Party; CI: confidence interval; Ctrl: control (multiple fractionated); Ev: events (pain relief); Trt: treatment (single fractionated).

Forest Plot 6.1.2. Pain Relief (“Complete or Partial Response”, Categorical) Single vs. Multiple Fractionated Radiotherapy

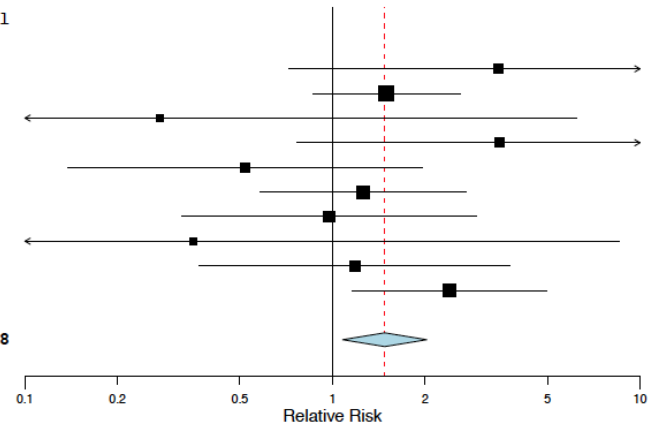
Studies	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
Altundag 2002	0.892 (0.635, 1.253)	13/17	12/14
AmouzegarHashemi 2008	1.206 (0.867, 1.677)	21/27	20/31
Anter 2015	1.000 (0.786, 1.273)	33/44	33/44
Badzio 2003	0.987 (0.845, 1.154)	53/64	52/62
BPTWP 1999	1.002 (0.925, 1.086)	274/351	257/330
Chow 2014	0.882 (0.737, 1.056)	116/258	134/263
Cole 1989	1.034 (0.769, 1.391)	14/16	11/13
Foro 1998	0.884 (0.690, 1.131)	19/25	43/50
Foro Arnalot 2008	1.051 (0.832, 1.328)	51/78	51/82
Gaze 1997	0.939 (0.849, 1.037)	108/129	99/111
Gutierrez Bayard 2014	0.909 (0.693, 1.193)	30/45	33/45
Hamouda 2007	0.950 (0.813, 1.110)	42/50	46/52
Hartsell 2005	0.984 (0.874, 1.109)	187/288	188/285
Kagei 1990	0.929 (0.712, 1.211)	12/14	12/13
Koswig 1999	0.964 (0.799, 1.163)	41/52	45/55
Nielsen 1998	0.885 (0.681, 1.149)	52/106	56/101
Ozsaran 2001	0.961 (0.767, 1.202)	27/36	57/73
Roos 2005	0.850 (0.708, 1.020)	73/119	83/115
Safwat 2007	0.966 (0.684, 1.363)	14/20	29/40
Sarkar 2002	0.908 (0.654, 1.260)	13/17	16/19
van der Linden 2004	0.974 (0.905, 1.049)	395/556	396/543
Overall (I²=0 %, P=0.989)	0.965 (0.932, 0.998)	1588/2312	1673/2341



Abbreviations: BPTWP: Bone Pain Trial Working Party; CI: confidence interval; Ctrl: control (multiple fractionated); Ev: events (pain relief);

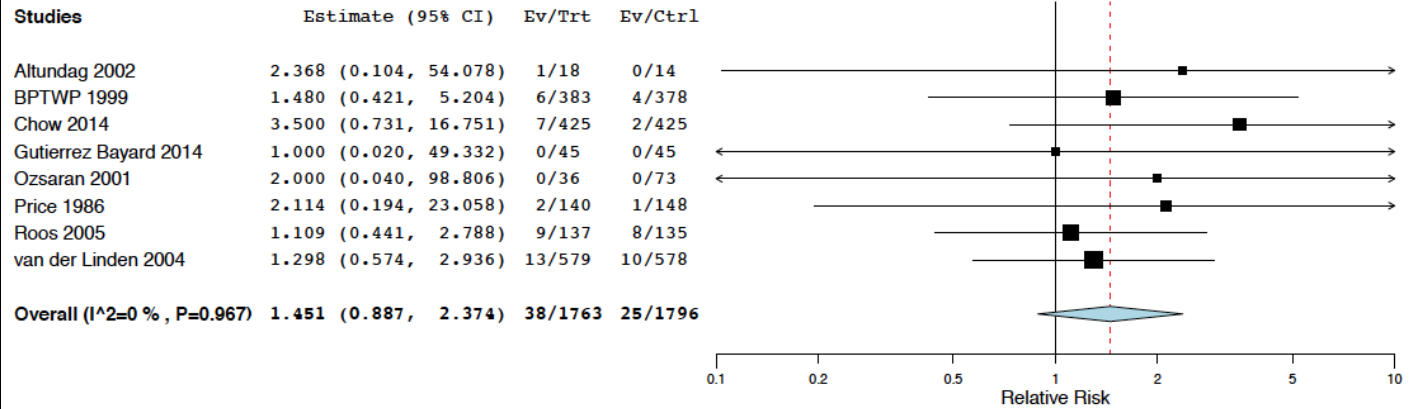
Forest Plot 6.1.3. Skeletal Related Events (Pathological Fracture at Index Site) Single vs. Multiple Fractionated Radiotherapy

Studies	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
BPTWP 1999	3.454 (0.722, 16.521)	7/383	2/378
Chow 2014	1.500 (0.866, 2.599)	30/425	20/425
Cole 1989	0.275 (0.012, 6.226)	0/16	1/13
Gutierrez Bayard 2014	3.500 (0.768, 15.942)	7/45	2/45
Hamouda 2007	0.520 (0.137, 1.967)	3/50	6/52
Hartsell 2005	1.259 (0.582, 2.727)	14/288	11/285
Nielsen 1998	0.975 (0.324, 2.939)	6/122	6/119
Price 1986	0.352 (0.014, 8.575)	0/140	1/148
Roos 2005	1.182 (0.370, 3.783)	6/137	5/135
van der Linden 2004	2.396 (1.156, 4.965)	24/579	10/578
Overall (I²=0%, P=0.421)	1.478 (1.078, 2.027)	97/2185	64/2178



Abbreviations: *BPTWP*: Bone Pain Trial Working Party; *CI*: confidence interval; *Ctrl*: control (multiple fractionated); *Ev*: events (skeletal related event); *Trt*: treatment (single fractionated).

Forest Plot 6.1.4. Skeletal Related Events (Spinal Cord Compression at Index Site) Single vs. Multiple Fractionated Radiotherapy



Abbreviations: *BPTWP*: Bone Pain Trial Working Party; *CI*: confidence interval; *Ctrl*: control (multiple fractionated); *Ev*: events (skeletal related event); *Trt*: treatment (single fractionated).

ACCEPTABILITY & PREFERENCES	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Major variability <input type="checkbox"/></p> <p>Minor variability <input checked="" type="checkbox"/> Yes</p> <p>Uncertain <input type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	<p><u>Research evidence</u> Single dose radiotherapy, where a patient receives a larger single dose (e.g. a 8Gy fraction) in a single clinic visit, is less expensive in terms of both time and money than a longer schedule where a patient receives smaller individual doses but an overall greater amount of radiotherapy split over several visits (e.g. 20-30 Gy given over 5-10 fractions)¹⁹². Prices vary widely due to global variation in the price of services. With negligible clinical differences, patients would probably prefer single dose therapy.</p> <p><u>Additional considerations</u> Private clinics may prefer to deliver multiple dose radiotherapy as it delivers greater profits, but, overall, key stakeholders accept the option.</p>
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FEASIBILITY ./ RESOURCE USE	<p>How large are the resource requirements?</p> <p>Major Minor Uncertain</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/></p>	<table border="1"> <thead> <tr> <th></th> <th colspan="3">Price (USD) from studies cited in ¹⁹²</th> </tr> <tr> <th></th> <th>Median</th> <th>Minimum</th> <th>Maximum</th> </tr> </thead> <tbody> <tr> <td>Single dose</td> <td>\$ 998</td> <td>\$ 222</td> <td>\$ 2438</td> </tr> <tr> <td>Multiple dose</td> <td>\$ 2316</td> <td>\$ 724</td> <td>\$ 3311</td> </tr> </tbody> </table>		Price (USD) from studies cited in ¹⁹²				Median	Minimum	Maximum	Single dose	\$ 998	\$ 222	\$ 2438	Multiple dose	\$ 2316	\$ 724	\$ 3311
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	Median	Minimum	Maximum															
Single dose	\$ 998	\$ 222	\$ 2438															
Multiple dose	\$ 2316	\$ 724	\$ 3311															
<p>Is the option feasible to implement?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/></p>	<p>If more patients were to be given single dose therapy, in settings where there is a shortage of radiation equipment and staff, the same resources could be used for greater coverage, as well as having lower costs to patients such as travel, making the single dose option the most feasible.</p>																	
	<p>Would the option improve equity in health?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/></p>	<p><u>Research evidence</u></p> <p>None</p> <p><u>Additional considerations</u></p> <p>As for resource and feasibility considerations above, if more patients were to be given single dose therapy, in settings where there is a shortage of radiation equipment and staff, the same resources could be used for greater coverage, as well as having lower costs to patients such as travel, making the single dose option the most feasible</p>																

Recommendation	<p>Current recommendation: None.</p> <p>New (draft) recommendation: In adults (including older persons) and adolescents with pain related to bone metastases, single-fraction (single dose) radiotherapy should be used when radiotherapy is indicated.</p>
Strength of Recommendation	Strong
Quality of Evidence	<p>➤ HIGH/MODERATE [Pain relief (critical) = high (categorical), low (continuous) Pain relief speed (critical) = moderate Pain relief maintenance (critical) = moderate Skeletal-related events, pathological fracture (important) = high Skeletal-related events, spinal cord compression (important) = high QoL (important) = low Functional outcomes (important) = low Acute bone flare (important) = low]</p>
Justification	<p>The choice of low-fractionated (single dose) or high-fractionated (multiple dose) radiotherapy makes little or no difference in bone pain relief, but high-fractionated (multiple dose) radiotherapy reduces the risk of pathological fractures and spinal compression at the index sites. The choice of radiotherapy schedule probably makes little or no difference in speed or duration of pain relief. The choice of radiotherapy schedule may make little or no difference in quality of life or functional status. Low-fractionated (single dose) radiotherapy may cause more acute bone flares than high-fractionated (multiple dose) radiotherapy. Therefore the negligible clinical differences between the schedules and the large cost and equity benefits possible, single dose should be used in favour of multiple dose radiotherapy where indicated. This means it should be used for people already with painful metastases, not for their prevention.</p>
Subgroup considerations	

Implementation considerations
[incl. M&E]

Research priorities
