Evidence Profile 6.1. Single Fractionated vs. Multiple Fractionated Radiotherapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single fractionated**	**Multiple fractionated**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain relief (categorical) (complete response, follow up: range 1 to 12 months)												
18 [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18]	RCT	not serious	not serious	not serious	not serious	none	568/2232 (25.4%)	562/2178 (25.8%	**RR 0.97** (0.89, 1.06)	**8 fewer per 1000** (from 28 fewer to 15 more)	High	CRITICAL
Pain relief (categorical) (improvement [complete or partial response], follow up: range 1 to 12 months)												
21 [1,2,3,4,5,6,7,8,9,10,11,12,13,14,16,17,18,19,20,21,22]	RCT	not serious	not serious	not serious	not serious	none	1588/2312 (68.7%)	1673/2341 (71.5%)	**RR 0.97** (0.93, 0.998)	**21 fewer per 1000** (from 48 to 1 fewer)	High	CRITICAL
Pain relief (continuous) (follow up: range 1 to 11 months; assessed with: VAS, NRS; Scale: 0 to 100 [worst] [A])												
3 [2,7,22]	RCT	not serious	not serious	not serious	serious [B]	Insufficient data for analysis	125	133	**HR 0.99** (0.51, 1.91) **Diff -5 to 2.5** (NS)		Low	CRITICAL
Pain relief speed												
3 [5,7,23]	RCT	not serious	not serious	not serious	serious [C]	none	597	598	NS [C]		Moderate	CRITICAL
Pain reduction maintenance												
9 [4,7,8,9,10,14,15,16,18]	RCT	not serious	not serious	not serious	not serious	Insufficient data for analysis	1201	1192	**HR 0.91** (0.46, 1.82) [D] **Diff 0 to -2 mo** [D] (NS)		Moderate	CRITICAL
Skeletal-related events (Fracture at index site, follow up: range 1 to 12 months)												
10 [5,6,9,10,11,14,15,16,19,24]	RCT	not serious	not serious	not serious	not serious	none	97/2185 (4.4%)	64/2178 (2.9%)	**RR 1.48** (1.08, 2.03)	**21 more per 1000** (from 4 to 46 more)	High	IMPORTANT
Skeletal-related events (Spinal cord compression at index site, follow up: range 2 to 12 months)												
8 [1,5,6,9,15,16,21,24]	RCT	not serious	not serious	not serious	not serious	none	38/1763 (2.2%)	25/1796 (1.4%)	**RR 1.45** (0.89, 2.37)	**10 more per 1000** (from 2 fewer to 30 more)	High	IMPORTANT
Quality of life: Improved (follow up: 1-2 months; assessed with: QLQ-C30 Global, Spitzer Index, Global QoL)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single fractionated**	**Multiple fractionated**	**Relative (95% CI)**	**Absolute (95% CI)**		
3 [6,8,14]	RCT	not serious	not serious	very serious [E]	not serious	none	118/336 (35%) improved 129 (continuous measure)	115/335 (34%) improved 111 continuous	**RR 1.02** (0.83, 1.26) **Diff 0** (nd)	**8 more per 1000** (from 58 fewer to 89 more)	Low	IMPORTANT
Functional outcomes: Physical, improved (follow up: 1.5-6 months; assessed with: QLQ-C30 Physical, Karnofsky performance status, Barthel index of ADL, "Performance status")												
4 [6,9,19,22]	RCT	not serious	not serious	very serious [F]	not serious	none	111/270 (41%) improved 45 (continuous measure)	116/293 (40%) improved 45 (continuous measure)	**RR 1.11** (0.84, 1.46) **Diff -0.6 mo** (-2.8, 1.6)	**43 more per 1000** (from 63 fewer to 182 more)	Low	IMPORTANT
Functional outcomes: Social, improved (follow up: 2 months; assessed with: QLQ-C30 social)												
1 [6]	RCT	not serious	N/A	very serious [G]	not serious	single study	101/232 (44%)	106/238 (45%)	**RR 0.98** (0.80, 1.20)	**10 fewer per 1000** (from 88 more to 90 fewer)	Very Low	IMPORTANT
Adverse events: Acute bone flare (severe flare, follow-up: 2 months)												
1 [16]	RCT	not serious	N/A	not serious	serious [H]	single study	7/137 (5.1%)	2/135 (1.5%)	**RR 3.45** (0.73, 16.3)	**36 more per 1000** (from 6 fewer to 78 more)	Very Low	IMPORTANT

***Abbreviations: CI**: confidence interval; **Diff**: difference (between groups); **EORTC**: European Organisation for Research and Treatment of Cancer; **GI**: gastrointestinal; **N/A**: not applicable; **NS**: not statistically significant; **NRS**: Numeric Rating Scale; **RCT**: randomized controlled trial(s); **RR**: relative risk (log scale); **VAS**: Visual Analog Scale.*

Explanations

A. Scales transformed to 0 to 100, as necessary.
B. Single study reported hazard ratio; Others report means or medians and "nonsignificant" difference.
C. Bone Pain Trial Working Party 1999: logrank difference P = 0.6; Foro Arnalot 2008: logrank difference P = 0.48; Meeuse 2010: 2 vs 2 weeks P=0.54.
D. Hazard ratio reported in one study (Roos 2005). All trials, explicitly or implicitly, reported no significant difference in duration but with insufficient data to allow meta-analysis.
E. QLQ-C30 and Spitzer Index are measures of quality of life that mix concepts of both quality of life and functional outcomes. "Global QoL" was undefined.
F. Karnofsky and Barthel Index are measures of functional status that mix concepts of both quality and functional outcomes. "Performance status" was undefined,
F. QLQ-C30 is a measure of functional status that mix concepts of both quality and functional outcomes.
H. Fewer than 300 participants.

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