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Review Article

Single vs multiple fraction palliative radiation therapy for bone metastases: Cumulative meta-analysis

Ronald Chow [a,b,*], Peter Hoskin [c,d], Steven E. Schild [e], Srinivas Raman [f], James Im [a], Daniel Zhang [a], Stephanie Chan [b], Nicholas Chiu [b], Leonard Chiu [b], Henry Lam [b], Edward Chow [b], Michael Lock [a]

[a] London Regional Cancer Program, London Health Sciences Centre, University of Western Ontario, London; [b] Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Canada; [c] Mount Vernon Hospital, London; [d] University of Manchester, United Kingdom; [e] Mayo Clinic, Scottsdale, USA; and [f] British Columbia Cancer Agency Vancouver Centre, Canada

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ABSTRACT

Introduction: There has been a long-standing debate regarding the efficacy of single fraction radiotherapy (SFRT) compared to multiple fraction radiotherapy (MFRT); many systematic reviews and meta-analyses have been conducted to resolve the debate and suggested SFRT is equally as effective as MFRT. Given the adequate amalgamated sample size that exists, it is difficult to appreciate the need for further RCTs. The aim of this paper was to conduct a cumulative meta-analysis to determine whether further trials will be of value to the meta-conclusion. This paper also assessed publication quality.

Methods: A total of 29 studies were used in our meta-analysis. Comprehensive Meta-Analysis (Version 3) by Biostat was used to conduct a cumulative meta-analysis. The Cochrane Risk of Bias assessment tool was employed to assess study quality of the included RCTs. Funnel plots were generated using Review Manager (RevMan 5.3) by Cochrane IMS, to visually assess for publication bias.

Results: All but one endpoint, overall response rates in assessable patients, maintained the same meta-conclusion over publication time; published studies did not change the amalgamated scientific conclusion of existing literature. Additional studies have simply confirmed pre-existing conclusions and refined the point estimate of the efficacy estimate. The majority of included studies have low risk of bias.

Conclusion: In conclusion, the meta-conclusion has remained consistent over time – SFRT is equally as efficacious as MFRT. Recent studies have had little impact on the overall conclusion, and given the vast amount of resources to execute a randomized trial, future resources should not be used to repeat these studies, and can be better allocated to test other hypotheses.

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Pain originating from uncomplicated bone metastases, defined as those which have not resulted in and are not at imminent risk for pathological fracture or spinal cord compression, is effectively palliated by conventional external beam radiation therapy (RT) [1,2]. There has been a long-standing debate regarding the efficacy of single fraction (SFRT) compared to multiple fraction RT (MFRT); many systematic reviews and meta-analyses have been conducted to date to try to resolve the debate [3–5]. More recent reviews by Chow et al. have even explored the optimal RT dose in both the SFRT and MFRT settings [6,7].

The most recent of these reviews, published by Rich et al. in 2018, reported that SFRT has similar outcomes to MFRT in pain control and toxicities [5]. This conclusion reaffirms previously published reviews [3,4] and is reflected in the guidelines published by Choosing Wisely Canada and United States, and the American Society for Therapeutic Radiology and Oncology [8–10]. Since the reviews dating back to 2007 and the publication of guidelines, new randomized controlled trials (RCTs) have still been conceived and published [11–15]. Given the adequate amalgamated sample size that exists (34 RCTs by Rich et al. [5]), it is difficult to appreciate the need for further RCTs. One may postulate that these more recent RCTs are conducted to try to further convince the global community about the equivalent efficacy of SFRT, as SFRT is not widely practiced, globally, and MFRT continues to be frequently implemented [16]. Some have argued that data are insufficient for major concerns, such as risk of cord compression and fracture risk, as a reason to use MFRT. Concerns over bias of prior papers may also be valid, as the earlier systematic reviews [3–5] did not assess publication quality of papers. There hence exists a need for a cumulative meta-analysis and risk of bias assessment, to definitively determine whether further trials in this field are

* Corresponding author at: c/o Dr Michael Lock, London Health Sciences Centre, University of Western Ontario, 800 Commissioners Road East, London, ON N6A 5W9, Canada.
E-mail address: rchow48@uwo.ca (R. Chow).

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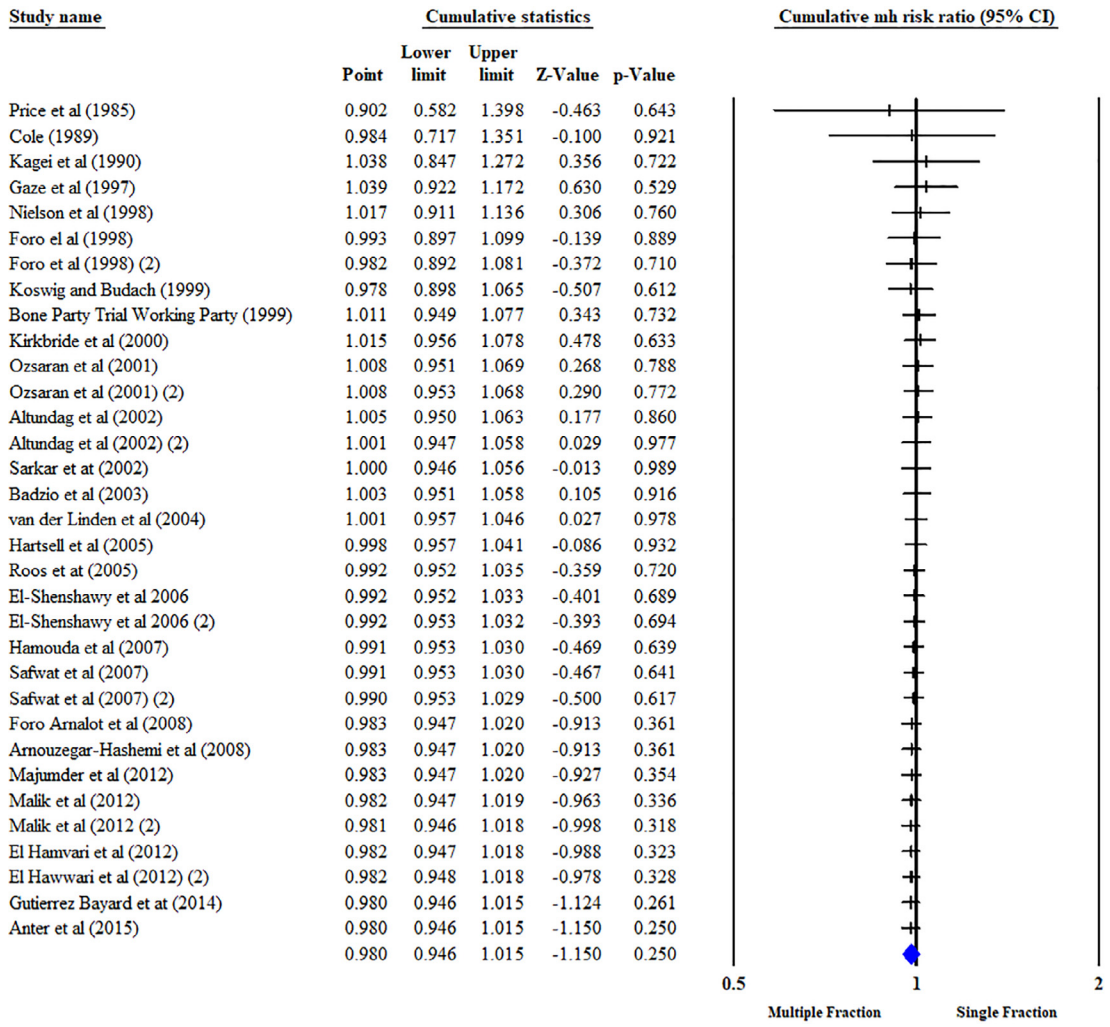

Fig. 1. Overall response rates for single versus multiple fractions for patients in the intention-to-treat analysis.

needed and also whether past trials are sufficient or appropriate to serve as a solid foundation of knowledge.

The aim of this paper was to conduct a cumulative meta-analysis to determine whether further trials will be of value to the meta-conclusion. Additionally, this paper attempted to assess publication quality.

Methods

Included studies

Papers included for this meta-analysis are the same as those included by Rich et al. in 2018 [5], who conducted a literature search, and conducted title & abstract and full-text screening to assess eligibility for inclusion as per PRISMA guidelines. A total of 29 studies [11–39] were used in our meta-analysis, with the same endpoints as those previously reported used here – rates of complete and overall response (as reported and defined by trials), re-treatment, pathological fracture, acute toxicity and spinal cord compression.

Statistical analysis

Comprehensive Meta-Analysis (Version 3) by Biostat was used to conduct a cumulative meta-analysis. The Mantel–Haenszel model was applied, with a random effects analysis model. Risk ratios (RR) and their accompanying 95% confidence intervals (CIs) were computed. Analyses were carried out, by intention-to-treat and assessable patients' analyses.

Assessment of publication quality

The Cochrane Risk of Bias assessment tool [40] was employed to assess study quality of the included RCTs. Funnel plots were generated using Review Manager (RevMan 5.3) by Cochrane IMS, to visually assess for publication bias.

Results

Intention-to-treat analysis

Over publication time, the meta-conclusion has remained unchanged that SFRT and MFRT are equivalent in efficacy for overall response rates, complete response rates, pathological fracture rates, spinal cord compression rates, and spinal cord compression rates for patients with spinal metastases. With respect to re-treatment rates, the conclusion is also unchanged over publication time; MFRT is superior to SFRT (Figs. 1–6).

Assessable patients

In 2007, the meta-conclusion shifted from not favouring either fractionation to favouring MFRT over SFRT in the setting of overall response rates. SFRT and MFRT are equivalent in terms of complete

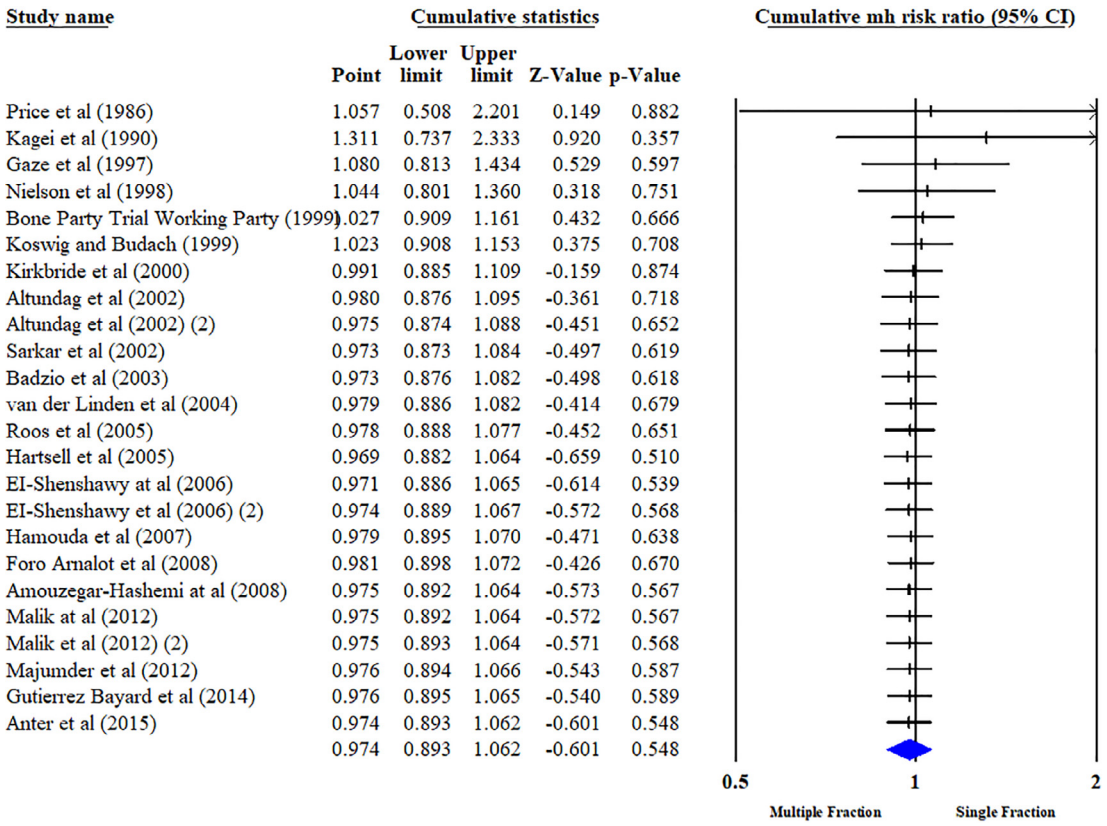

Fig. 2. Complete response rates for single versus multiple fractions for patients in the intention-to-treat analysis.

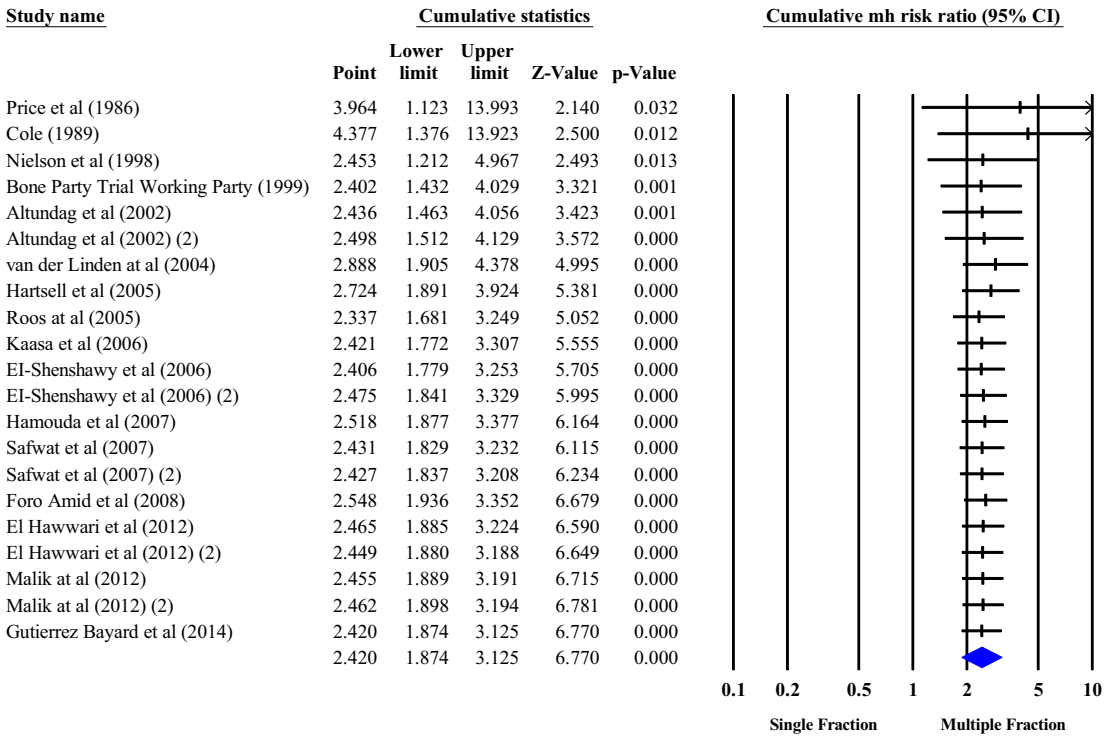

Fig. 3. Re-treatment rates for single versus multiple fractions for patients in the intention-to-treat analysis.

response rates, pathological fracture rates, spinal cord compression rates, and spinal cord compression rates in patients with spinal metastases; this conclusion has remained consistent over publication time. Higher re-treatment rates have always been observed for SFRT over publication time (Supplementary Material 1–6).

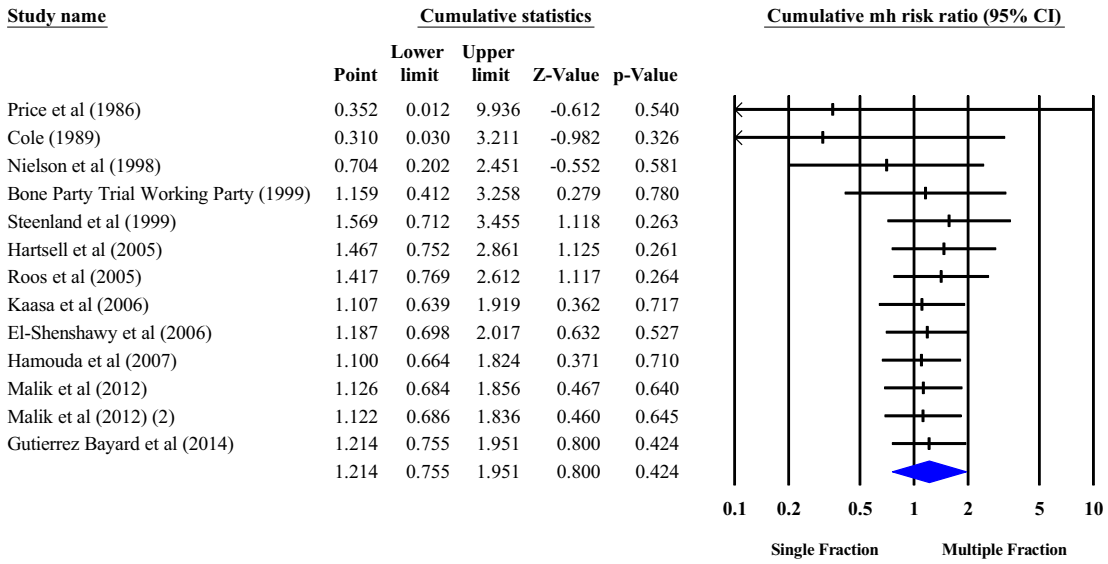

Fig. 4. Pathological fracture rates for single versus multiple fractions for patients in the intention-to-treat analysis.

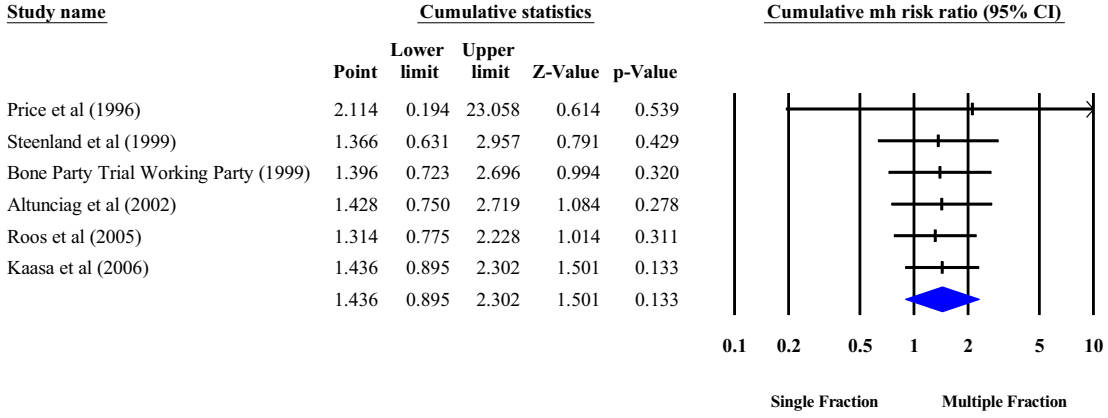

Fig. 5. Spinal cord compression rates for single versus multiple fractions for patients in the intention-to-treat analysis.

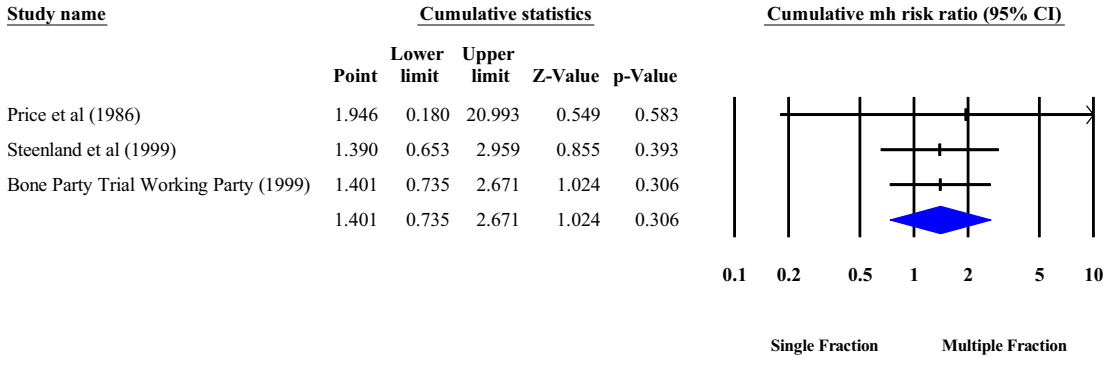

Fig. 6. Spinal cord compression rates for single versus multiple fractions for patients with spinal metastases in the intention-to-treat analysis.

Assessment of bias

There exists some concern for publication bias for the endpoint of re-treatment rates, in both the ITT and assessable-patients analysis. No other obvious publication biases exist in other endpoints (Supplementary Material 7–18). Most of the studies had a low risk of bias, according to the Cochrane Risk of Bias assessment tool (Supplementary Material 19).

Discussion

The purpose of this paper was to critically appraise the literature to see the impact of publications on the meta-conclusion and determine whether further studies are warranted. All but one endpoint, overall response rates in assessable patients, has maintained the same meta-conclusion over publication time; pub-

lished studies did not change the amalgamated scientific conclusion of existing literature. Nevertheless, the overall response rates in all patients analysed by intention-to-treat remains the gold standard in RCTs, for which the meta-conclusion has not changed with the addition of trials. Additional studies have simply confirmed pre-existing conclusions and refined the point estimate of the efficacy estimate. Given the extensive resources required to conduct a RCT, resources may be used elsewhere as additional studies addressing this issue will add little value to existing literature.

With respect to re-treatment rates and overall response in assessable patients, MFRT is more efficacious than SFRT. There seems to exist a publication bias in the retreatment setting, with visual assessment of funnel plot suggesting a skew towards more studies reporting MFRT as more efficacious and very few documenting SFRT is more efficacious in this setting. However, assessment of biases using Cochrane Risk of Bias assessment tool suggests that these studies, overall, have a low risk of bias. Such a conclusion of publication bias from the funnel plots may hence reflect the fact that the majority of studies are measuring the true superiority of MFRT over SFRT in decreasing retreatment rates. Alternatively, the apparent superiority may be a reflection of clinical practices where radiation oncologists are more reluctant to retreat after higher dose-fractionated schedules rather than a product of publication bias.

This study was not without limitations. A meta-analysis suffers from constraints and biases intrinsic to designs of individual study RCTs. Assessment of publication bias only involved visual assessment of funnel plots and lacked any quantitative statistical test such as Egger's test. There existed no obvious visual evidence of bias, and hence Egger's test was not utilized in this study.

In conclusion, the meta-conclusion has remained consistent over time – SFRT is equally as efficacious as MFRT for most endpoints tested. Recent studies have had little impact on the overall conclusion, and given the vast amount of resources to execute a RCT, future studies should not be conducted addressing this issue. Future resources and funding could be better allocated to test other hypotheses (i.e. complicated bone metastases).

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.06.037.

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