A critical appraisal of the four systematic reviews and meta-analysis on stereotactic body radiation therapy versus external beam radiotherapy for painful bone metastases and where we go from here[※]

Henry C. Y. Wong[1#^], Adrian Wai Chan[2#], Peter Johnstone[3], Charles B. Simone II[4], Inmaculada Navarro-Domenech[5], Peter Hoskin[6,7], Candice Johnstone[8], Abram Recht[9], Johan Menten[10], Yvette M. van der Linden[11,12], Joanne M. van der Velden[13], Quynh-Nhu Nguyen[14], Stephen Lutz[15], Nicolaus Andratschke[16], Jonas Wilmann[16], Joanna Kazmierska[17,18], Mateusz Spalek[19,20], Fiona Lim[1], H. Michael Yu[3], Brad Perez[3], Gustavo Nader Marta[21,22], Vassilios Vassiliou[23], Shing Fung Lee[2,24], Pierluigi Bonomo[25], Agata Rembielak[26,27], Edward Chow[28], Eva Oldenburger[10*], Srinivas Raman[5*]

[1]Department of Oncology, Princess Margaret Hospital, Hong Kong SAR, China; [2]Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong SAR, China; [3]Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [4]Department of Radiation Oncology, New York Proton Center, New York, NY, USA; [5]Radiation Medicine Program, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada; [6]Mount Vernon Cancer Centre, Northwood, UK; [7]Division of Cancer Sciences, The University of Manchester, UK; [8]Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI, USA; [9]Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA; [10]Department of Radiation Oncology, University Hospital Leuven, Leuven, Belgium; [11]Department of Radiotherapy, Leiden University Medical Centre, Leiden, The Netherlands; [12]Centre of Expertise in Palliative Care, Leiden University Medical Centre, Leiden, The Netherlands; [13]Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands; [14]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [15]Eastern Woods Radiation Oncology, Blanchard Valley Health Organization, Findlay, OH, USA; [16]Department of Radiation Oncology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [17]Radiotherapy Department II, Greater Poland Cancer Centre, Poznan, Poland; [18]Department of Electroradiology, Poznań University of Medical Sciences, Poznan, Poland; [19]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [20]Department of Radiotherapy I, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [21]Department of Radiation Oncology, Hospital Sírio-Libanês, São Paulo, Brazil; [22]Latin America Cooperative Oncology Group (LACOG), Porto Alegre, Brazil; [23]Department of Radiation Oncology, Bank of Cyprus Oncology Centre, Nicosia, Cyprus; [24]Department of Radiation Oncology, National University Cancer Institute, National University Hospital, Singapore, Singapore; [25]Department of Oncology, Azienda, Ospedaliero-Universitaria Careggi, Florence, Italy; [26]Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK; [27]Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK; [28]Department of Radiation Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada

Contributions: (I) Conception and design: HCY Wong, AW Chan, E Chow, CB Simone 2nd, E Oldenburger, S Raman; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

#These authors contributed equally to this work and should be considered as co-first authors.

*These authors contributed equally to this work.

Correspondence to: Dr. Henry C. Y. Wong. Department of Oncology, Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Lai Chi Kok, Kowloon, Hong Kong SAR, China. Email: henrywong3011@gmail.com.

Ann Palliat Med 2023;12(6):1318-1330 | https://dx.doi.org/10.21037/apm-23-218

Abstract: Radiotherapy is an important treatment modality for pain control in patients with bone metastases. Stereotactic body radiation therapy (SBRT), which allows delivering a much higher dose per fraction while sparing critical structures compared to conventional external beam radiotherapy (cEBRT), has become more widely used, especially in the oligometastatic setting. Randomized controlled trials (RCTs) comparing the pain response rate of SBRT and cEBRT for bone metastases have shown conflicting results, as have four recent systematic reviews with meta-analyses of these trials. Possible reasons for the different outcomes between these reviews include differences in methodology, which trials were included, and the endpoints examined and how they were defined. We suggest ways to improve analysis of these RCTs, particularly performing an individual patient-level meta-analysis since the trials included heterogeneous populations. The results of such studies will help guide future investigations needed to validate patient selection criteria, optimize SBRT dose schedules, include additional endpoints (such as the time to onset of pain response, durability of pain response, quality of life (QOL), and side effects of SBRT), and better assess the cost-effectiveness and trade-offs of SBRT compared to cEBRT. An international Delphi consensus to guide selection of optimal candidates for SBRT is warranted before more prospective data is available.

Keywords: Pain; stereotactic body radiation therapy (SBRT); bone metastasis; conventional external beam radiotherapy (cEBRT)

Introduction

Bones are one of the most common sites of distant metastasis in advanced malignancies (1). The incidence of patients with bone metastases is likely to increase with continued advances in systemic therapy (2). Bone metastases commonly present with pain, which can be debilitating and may significantly affect quality of life (QOL) (3). Conventional external beam radiotherapy (cEBRT) has been used to treat patients with painful bone metastases for decades (4). Radiation is effective in alleviating pain in patients with bone metastases because it kills off tumour cells and deactivates osteoclasts, which in turn stabilizes the bones and reduces the pressure effect on surrounding nerves (4). Many radiation doses and schedules have been used, with none of them showing superiority over another with regards to pain response (5,6).

Since the pooled overall pain response of cEBRT is around 60% (5,7), there has been interest whether dose escalation can result in a higher pain response. Highly conformal radiation techniques, such as stereotactic body radiation therapy (SBRT), allow delivery of a much higher dose per fraction to a target while sparing the critical structures nearby (8). Seven randomized controlled trials (RCTs) using SBRT have been performed to date, all with different inclusion criteria, study endpoints and radiation treatment schedules (9-15). Unfortunately, their results are somewhat conflicting. For example, the RCT by Sahgal *et al.* demonstrated superiority of SBRT, whereas that by Pielkenrood *et al.* did not (11,14).

The American Society for Radiation Oncology (ASTRO) evidence-based guideline on palliative radiation therapy for bone metastases published in 2017 suggested that SBRT should be considered only in a trial setting (16). Similarly, the 2022 European Society for Radiotherapy and Oncology (ESTRO) guidelines for patients with uncomplicated bone metastases also recommended that there is not enough evidence for routine use of SBRT in patients with painful bone metastases (17).

Four systematic reviews comparing SBRT versus cEBRT for patients with previously unirradiated painful bone metastasis were published in 2022 (18-21). Two of these reviews reported a benefit of SBRT over cEBRT in overall pain response at 3 months (18,20), whereas the other two did not (19,21).

This clinical practice review aims to discuss the conclusions of and discrepancies between the systematic reviews, how the radiation oncology community should use these results in clinical practice, and how future research should be performed to better define the role of SBRT in the treatment of bone metastases.

Table 1 Primary and secondary end points of systematic reviews

Study endpoint	Ito *et al.* (19)	Lee *et al.* (21)	Song *et al.* (18)	Wang *et al.* (20)
Primary endpoint	OR rate at 3 months (intention to treat analysis)	OR rate at 3 months	Pain relief (OR and CR rates at 1, 3 and 6 months)	OR rate at 3 months
Secondary endpoints	OR rate at 3 months of only evaluable patients	CR rate at 3 months	Pain score change	OR rate at 1 month
	CR rate at 3 months	OR rate at 6 months	Local progression free survival	OR rate at 6 months
	OR rate at 6 months	CR rate at 6 months	Re-irradiation rate	Oral morphine equivalent dose
	Adverse events	Local progression rate	RT-related side effects	Adverse events
	Quality of life	Overall survival		
		Adverse events		
		Quality of life		

OR, overall pain response; CR, complete pain response; RT, radiotherapy.

Table 2 Included randomised control trials in systematic reviews

Primary endpoint [author, year]	Ito *et al.* (19)	Lee *et al.* (21)	Song *et al.* (18)	Wang *et al.* (20)
Pain response according to ICPRE on VAS at 1 month [Berwouts *et al.* 2015 (9)]	√	×	√	×
Pain relief of >2 points on VAS at 3 months [Sprave *et al.* 2018 (10)]	√	√	√	√
Pain response according to ICPRE on a 0 to 10 pain scale [Nguyen *et al.* 2021 (12)]	√	√	√	√
Pain relief of 3 points on NRS at 3 months [Ryu *et al.* 2019 (abstract form) (13)]	√	√	×	×
Pain response according to ICPRE on NRS at 3 months [Pielkenrood *et al.* 2021 (14)]	√	√	√	√
Pain relief on NRS at 3 months [Sakr *et al.* 2020 (15)]	√	√	√	×
Complete pain response according to ICPRE on BPI pain score at 3 months [Sahgal *et al.* 2021 (11)]	√	√	√	√

√, SBRT better; ×, SBRT worse. ICPRE, International Consensus on Palliative Radiotherapy Endpoints; VAS, visual analogue scale; NRS, numerical rating scale; BPI, brief pain inventory; SBRT, stereotactic body radiation therapy.

Study design of the systematic reviews

All four reviews used overall pain response at 3 months as their primary endpoint (18-21). Overall pain response and complete pain response at other time points were studied as co-primary endpoints by Song *et al.* (18), whereas they were secondary endpoints in the publications of Lee *et al.* and Ito *et al.* (19,21). Adverse events were assessed as secondary endpoints in all four studies. Lee *et al.* and Ito *et al.* also assessed local control and QOL as secondary endpoints (19,21) (*Table 1*).

Song *et al.* included RCTs, prospective cohort studies, and retrospective analyses in their systematic review. The inclusion of study designs other than RCTs could be problematic, as the documentation of pain response in these primary studies may be incomplete and could be done at varying timepoints, which cannot be directly compared. Song *et al.* addressed this point by performing a separate meta-analyses for all included studies and RCTs only (18). Only conclusions of the meta-analysis of RCTs by Song *et al.* will be discussed in this paper. The other three systematic reviews only included RCTs. *Table 2* summarises

RCTs that were included. It is important to highlight that the phase 3 RTOG 0631 trial by Ryu *et al.*, which is the largest such RCT comparing SBRT and cEBRT to date with 339 patients, has only been published in abstract form to date (13). An exploratory sensitivity analysis excluding Ryu *et al.* was performed by Lee *et al.*, but not by Ito *et al.* (19,21).

Ito *et al.* and Wang *et al.* performed meta-analyses of results using relative risk ratios (RR), whereas Lee *et al.* and Song *et al.* used odds ratio (OR) (18-21). Reporting using ORs in meta-analysis may overestimate the relative risk when the incidence of the endpoint is common (for example, more than 20%) (22). This may have affected the interpretation of the results.

Commentary on results of systematic reviews and meta-analyses

Pain response

Overall pain response at 3 months was superior for SBRT in the systematic reviews by Song *et al.* and Wang *et al.*, but not in those by Ito *et al.* and Lee *et al.* (18-21). The most likely reason for this difference is the inclusion of the negative RTOG 0631 trial of Ryu *et al.* by Ito *et al.* and Lee *et al.*, since it was heavily weighted due to its large sample size. Song *et al.* excluded RTOG 0631 from their analysis, on the basis that "only the abstract without primary endpoint was published" (18). The meta-analysis by Wang *et al.* did not give any specific reasons for excluding RTOG 0631 (20). An exploratory analysis by Lee *et al.* confirmed that if RTOG 0631 was excluded, SBRT would be associated with statistically significant benefit over cEBRT in overall pain response at 3 months (21).

Lee *et al.* noted the inclusion of patients with more severe pain in RTOG 0631 at baseline and its more stringent definition of partial pain response as possible reasons why the trial had negative findings, compared to other RCTs (21). The RTOG 0631 trial defined partial response as a reduction of worst pain score of 3 or more compared with baseline on a scale of 0 to 10. However, the other RCTs generally used the definition of the International Consensus on Palliative Radiotherapy Endpoints (ICPRE) (23,24), which characterises a partial pain response as a reduction of worst pain score of 2 points or more compared with baseline on a scale of 0 to 10 without increase in oral morphine equivalent consumption. However, it remains unclear whether the results of RTOG 0631 would be different using this more liberal definition.

Other reasons cited to explain the negative result of RTOG 0631 included the lower dose used (16 or 18 Gy single fraction; BED10: 41.6 or 50.4 Gy_{10}) compared with the dose in the RCT by Sprave *et al.* (24 Gy single fraction; BED10: 81.6 Gy_{10}) (10) and Sahgal *et al.* (24 Gy in 2 fractions; BED10: 52.8 Gy_{10}) (11). Another possible explanation is that the RTOG 0631 study allowed patients to have up to a total of three study segments in the spine, compared to only one in Sahgal *et al.*'s study and two in Sprave *et al.*'s (10,11,13,25). Treatment of non-study spine metastases was not permitted in RTOG 0631, whereas this was allowed in Sahgal *et al.*'s study at the discretion of the treating radiation oncologists (11,25). Coupled with patients' higher baseline pain score compared to the other studies, there is a possibility that patients in RTOG 0631 had more severe and extensive spinal disease, possibly contributing to spinal instability (26). An unstable spine results in mechanical pain on top of the pain from the studied spinal segments, resulting in the relative benefit of SBRT over cEBRT not being as pronounced in RTOG 0631. Although RTOG 0631 attempted to control for the confounding effect of spinal instability by recruiting patients with a spinal collapse of less than 50% and excluding those with vertebral compression fracture and bony retropulsion, this was not likely as sensitive as the Spinal Instability in Neoplasia Score (SINS) employed by Sahgal *et al.* (11,25), which has shown reliability and validity amongst both spine surgeons and radiation oncologists (27,28).

While the benefit of overall pain response at 3 months for SBRT was inconsistent among the four meta-analyses, SBRT resulted in more frequent complete pain response at 3 and 6 months in all three reviews that included it as an endpoint (18,19,21). However, the RTOG 0631 trial results for complete pain response at any time point have not yet been reported, and therefore the meta-analyses did not include it into their calculations. It is not known whether the same conclusion will be reached once RTOG 0631 is fully published. Wang *et al.* and Song *et al.* also studied pain response at 1 month (18,20). No differences were seen in the overall and complete pain responses in both studies. Future studies need to better characterise the time to pain response for the different radiation techniques. For some patients with intractable pain and a poor prognosis, having complete pain relief at 3 months after radiation treatment may not be meaningful. A possible way to understand patients' time to pain response is to use pain diaries or (abbreviated) patient-reported outcome measure tools.

The durability of pain relief after initial pain response is also important and arguably more clinically meaningful than assessing pain response at a specific time point. However, most existing studies that include duration of response as an endpoint considered competing events such as death and reirradiation as censored rather than events of interest and therefore may overestimate the results (29). Net Pain Relief, which is the proportion of remaining life spent with pain response, has been advocated to be an important endpoint in palliative radiotherapy for bone metastasis and could be used in future studies assessing SBRT (30).

One of the major potential advantages of systemic reviews is their greater power to perform subgroup analyses. For example, Lee *et al.* found that multiple-fraction SBRT regimens were more effective than single-fraction regimens and that the proportion of baseline pain scores 5 or higher had an impact on the OR of relief from SBRT (21). Song *et al.* showed that giving SBRT with static field intensity modulated radiation therapy (IMRT) instead of volumetric modulated arc therapy (VMAT), Novalis shaped beam therapy or Cyberknife had better analgesic effect, possibly due to more hot spots generated by the low homogeneity index of IMRT (18). However, subgroup findings between these systemic reviews also varied. Song *et al.* demonstrated that the analgesic advantage with SBRT was more pronounced with spinal lesions compared to non-spine lesions when all studies (including non-RCTs) were analysed. This observation was not seen when the subgroup analysis was performed in RCTs only (18). Ito *et al.* and Lee *et al.* also showed that the benefit of SBRT in patients with spine or non-spine lesions were not statistically different in their subgroup analysis (19,21). While the RCTs predominantly had patients with spine metastases, close to half (133 out of 267 patients, 49.8%) of the patients in the non-RCTs of the meta-analysis by Song *et al.* had non-spine bone metastases (18,31-34). The imbalance of patients between the spine and non-spine subgroups in the RCTs may be a reason why a difference was not shown.

Local progression

The secondary endpoint of local progression was included in the meta-analyse of Song *et al.* and Lee *et al.* (18,21). Lee *et al.* found that there was a significantly lower local progression rate in the SBRT group, based on the RCTs by Nguyen *et al.* and Sahgal *et al.* (OR =0.19; P<0.01) (11,12). Song *et al.* analyzed the local progression-free survival (PFS) of these two RCTs and showed that there was no statistical difference, but there was a trend towards better PFS in the SBRT group (pooled hazard ratio: 0.18, P=0.334) (18). Local progression rates may be a more appropriate endpoint than PFS for analyzing RCTs which contain patients with diverse tumour histologies, who receive many types of systemic treatments, and who have highly variable overall prognoses, as death may occur before local progression in patients with metastatic disease. The lower risk of local failure following SBRT was confirmed at longer follow-up of the cohort of patients previously enrolled in the study of Sahgal *et al.* (35).

Adverse events

The four meta-analyses consistently showed that the fracture rate was not increased in the SBRT group (18-21). However, the median follow-up ranged from 6 to 8.1 months among the RCTs which specified the duration of follow-up, and therefore this conclusion should be treated with caution (9-11,18-21). One hundred thirty seven patients treated with SBRT in the trial of Sahgal *et al.* were reviewed for long term complications (35). At a median follow up of 11.3 months, there was a trend towards an increased rate of iatrogenic vertebral compressive fracture (VCF) after SBRT compared with cEBRT (P=0.0866), with all of the five grade 3 VCF in the SBRT group (35). This suggests that the risk of VCF could become more apparent with longer follow-up and may be underestimated by the current meta-analyses.

In the meta-analysis by Lee *et al.*, patients in the SBRT group had a higher rate of pain flare (43%) compared to the cEBRT group (33%) (21). However, the definition of pain flare was not well defined in the individual RCTs. Sahgal *et al.*'s study specified pain flare as any patient-reported increase in pain that required dexamethasone during and up to 1 month after radiotherapy (11). More studies are needed to investigate the severity of pain flare and how it affects the QOL of patients.

The incidence of other adverse events of grade 2 or higher, such as nausea, fatigue, radiation dermatitis, and dysphagia, were similar between the two arms in the systematic reviews. No radiation myelopathy events were seen.

QOL

Westhoff *et al.* demonstrated that patients who have a pain response to radiotherapy have a better QOL (36). However,

Table 3 Summary of results of the four systematic review and meta-analysis of RCTs

Study outcome	Ito *et al.* (19)	Lee *et al.* (21)	Song *et al.* (18)	Wang *et al.* (20)
Pain relief				
OR rate at 1 month	–	–	~	–
CR rate at 1 month	–	–	~	–
OR rate at 3 months	~	~	√	√
CR rate at 3 months	√	√	√	–
OR rate at 6 months	~	~	√	~
CR rate at 6 months	–	√	√	–
Adverse events				
Pain flare	–	×	–	–
Fracture rate	~	~	~	~
Local progression	–	√ (local progression rate)	~ (local progression free survival)	–
Quality of life	~	~	–	–

–, not studied; ~, no difference; √, SBRT better; ×, SBRT worse. RCTs, randomized controlled trials; OR, overall pain response; CR, complete pain response; SBRT, stereotactic body radiation therapy.

other problems caused by bone metastases, such as impairments in mobility and performing activities of daily living, also affect patients' QOL and may not necessarily correlate with their level of pain (37,38). Hence, assessing QOL with a validated patient-reported tool may be more useful than performing pain assessment alone in evaluating the efficacy of treatments for bone metastases.

The systematic reviews by Ito *et al.* and Lee *et al.* included QOL as a secondary endpoint. Although they found complete pain response was improved with SBRT at 3 months, improvement in QOL was not consistently observed (19,21). Pielkenrood *et al.* and Ryu *et al.* even showed that patients who received cEBRT had a better QOL (13,39). However, different trials used different instruments to assess QOL. This makes the results harder to interpret, especially when viewed in combination with the heterogeneity in histologies, systemic treatments used, number of metastatic sites (both in bone and non-bone), and disease prognosis amongst study participants.

An additional confounding factor in assessing the benefits of SBRT to cEBRT is that the latter were performed using 2D or 3D conformal techniques. Randomised phase II studies using conventional radiotherapy schedules but different treatment techniques in the two arms have suggested that patients treated with VMAT for bone metastases had a better QOL than those treated with cEBRT, possibly because of its ability to give less radiation

dose to normal tissues and hence result in fewer side effects (40,41). The results of an ongoing multi-centre phase III study are eagerly awaited to confirm the improvement in QOL with these advanced techniques (42). Future studies that study QOL as a primary endpoint should consider comparing SBRT with cEBRT planned by IMRT/VMAT. QOL assessment tools also need to be updated to address the side effects of SBRT such as pain flare, compression fractures, and esophagitis (when treating cervical and thoracic spine metastases) (43,44).

Summary

The conclusions of the four systematic reviews are summarized in *Table 3*. The conflicting results and methodology of these trials result in uncertainty whether overall pain response at 3 months is better with SBRT than cEBRT. However, SBRT may result in a higher rate of complete pain response at 3 months and beyond and offer improved local control. Additionally, SBRT appears as safe as cEBRT at least in the short term, although SBRT may increase the risk of a pain flare.

Cost effectiveness of SBRT

SBRT is typically more expensive and more labour-intensive than cEBRT for several reasons. First, magnetic

Table 4 Number needed to treat for SBRT to produce one complete pain response relative to cEBRT

Study	cEBRT				SBRT				Absolute risk reduction	Number needed to treat
	CR number	Total number	CR%	Dose	CR number	Total number	CR%	Dose		
Sprave *et al.* 2018 (10)	4	23	17.40%	30 Gy/10 Fr	10	23	43.50%	24 Gy/1 Fr	26.10%	4
Sahgal *et al.* 2021 (11)	16	115	14%	20 Gy/5 Fr	40	114	35%	24 Gy/2 Fr	21%	5

SBRT, stereotactic body radiation therapy; cEBRT, conventional external beam radiotherapy; CR, complete pain response.

resonance imaging, which may not be conveniently available due to resource limitations, is often paramount to accurately delineate the tumour target and the organs at risk (8). Additionally, immobilisation devices are needed to avoid geographical miss, and sophisticated quality assurance programs are necessary to ensure the accuracy of dose calculations and delivery (8). Both of these may not be required to the same degree for cEBRT treatments. The estimated cost of spine SBRT based on the US national Medicare reimbursement rate for 2020 is US $9,400 and US $11,100 for single and two-fraction treatments respectively (45). These rates are more than double the cost of a five-fraction cEBRT treatment (US $4,330) and more than triple that of a single-fraction treatment (US $3,000) (45).

Kowalchuk *et al.* assessed the cost-effectiveness of SBRT using a cost-utility model, based on the estimates of cEBRT and SBRT to achieve complete pain response at 3 months in the studies of Sahgal *et al.* and Sprave *et al.* The incremental cost-effectiveness ratio (ICER) for two-fraction SBRT treatment compared to single-fraction cEBRT was US $194,145 per quality-adjusted life-year (QALY) gained, which was nearly double the commonly employed willingness-to-pay threshold of US $100,000 per QALY gained (45). Therefore, two-fraction SBRT was concluded to be not cost-effective. Single fraction SBRT had a lower treatment cost and was cost-effective with the ICER of US $92,833 per QALY gained (45). If two-fraction SBRT resulted in improved overall survival, the treatment becomes cost-effective after 3 months (45), suggesting appropriate patient selection for this treatment is essential.

Assessment of cost-effectiveness with ICER, however, does not address the opportunity costs incurred by SBRT (46). The additional manpower and machine time allocated for SBRT may affect some patients' access to timely treatment, although the time to perform SBRT treatments may vary depending on the treatment centres' prior experience with advanced radiation techniques. Oncology centres already

using IMRT or VMAT in the palliative or curative setting may find the burden of implementing SBRT to be modest, but the cost of introducing SBRT may be substantial in other centres where 2D or 3D conformal techniques are predominantly used. Therefore, resource allocation should be individualised for each cancer centre based on its expertise in performing advanced radiation techniques and its budget.

The number needed to treat (NNT) is an intuitive measure of the relative efficacy of different treatments and may help guide decisions on resource allocation (47). *Table 4* summarises the NNT for complete pain response at 3 months with SBRT, based on the randomised trials of treatment of spine metastases. Arifin *et al.* estimated that one-third of patients treated with cEBRT in a large-volume tertiary centre in Canada would be eligible for SBRT based on the inclusion criteria of Sahgal *et al.* (48). This could substantially increase the workload and resource utilisation for the treatment facility if all of these patients were treated with SBRT. Yet, based on the NNT, only 1 in 5 SBRT treatments would result in complete pain response beyond that expected from cEBRT. It is important that oncology centres perform comprehensive cost-benefit analyses specific to their capacity to carry out SBRT before routinely offering SBRT to every suitable patient. An example on how to employ this is to use league tables. This approach ranks all the available intervention based on their ICER in the form of a table and implements them beginning at the top of the league table until the budget is exhausted (49,50). Using this approach, the ICER of radiotherapy using 2D, IMRT/VMAT or SBRT can all be calculated and ranked. Whether SBRT should be adopted would depend on both its ICER and the size of the budget.

Although the randomised studies cannot be directly compared because of the different inclusion criteria and definitions for pain response, the lower number to treat for complete pain response at 3 and 6 months for Sprave *et al.*'s study may suggest that dose escalation could achieve greater

pain control relative to cEBRT. It should be highlighted that the vertebral compression fracture rates were however more than doubled in Sprave *et al.*'s study (27.8%) compared to Sahgal *et al.* (11%) (10,11). Delivering 24 Gy in only a single fraction (BED10 81.6 Gy) may have contributed to this increase. A retrospective analysis by Zeng *et al.* compared patients treated with 28 Gy in 2 fractions (BED10 67.2 Gy) to those treated with the schedule in Sahgal *et al.*'s study (24 Gy in 2 fractions, BED10 52.8 Gy) (51). This study demonstrated that this two-fraction high-dose regimen was associated with a lower risk of magnetic resonance imaging (MRI)-assessed local failures, while not increasing the risk of vertebral compression fractures. Prospective studies are needed to compare the efficacy and safety of a single-fraction dose scheme (for example, 21 Gy, BED10 65.1 Gy_{10}) to 24 Gy or 28 Gy delivered in 2 fractions.

Future research directions

Routinely using SBRT for all patients with painful bone metastases would add significant workload and cost to the health care system. Hence, it is very important to determine which patients benefit meaningfully from it.

Problems in analysing trials comparing SBRT to cEBRT include the need for longer follow-up, attention to more endpoints with uniform definitions, and performing subgroup analyses, as have been discussed above. Another major issue is to understand patients' preferences for the choice of radiation technique. For example, some of the immobilisation devices used to ensure a reproducible set-up for SBRT may be more uncomfortable for patients. Patients with a poor performance status or highly symptomatic disease may not be able to tolerate the longer treatment time of SBRT. Additionally, a relatively longer preparation time is required for SBRT treatment, which may result in patients in some centers needing to wait for weeks to begin radiation instead of days or hours. Patients may also develop higher rates of pain flare with SBRT. In the randomised trial by Pielkenrood *et al.*, 27% of patients randomised to the SBRT arm declined the offer of SBRT due to its less efficient planning logistics. For patients who consented to receive SBRT, 21% of them could not complete the treatment. Reasons for this included increased pain due to the long waiting time, severe pain flare after first treatment and inability to complete MRI planning due to pain (14). Hence, some patients may decide to receive cEBRT instead of SBRT, accepting a lower chance of complete pain response in the long term but quicker access

to radiation treatment, with the option of repeating cEBRT or SBRT later if there is suboptimal or short duration of pain response. It would be helpful to understand patients' preferences for treatment with a large-scale prospective survey and collect patient feedback on their experiences before, during and after SBRT.

Another unsettled issue is whether SBRT improves outcome for patients with non-spine bone metastases. The randomised phase II study by Nguyen *et al.* had the largest number of patients with non-spine bone metastases (154 patients) (12). This study showed that giving 12 or 16 Gy in a single fraction by SBRT was non-inferior to multi-fraction cEBRT (30 Gy in 10 daily fractions). The higher dose of 16 Gy was associated with a higher rate of pain control and improved local control (12,52). On the other hand, the randomised phase II study by Pielkenrood, which included 45% of patients with non-spine bone metastases, showed that SBRT did not improve pain response (14). One can argue that pain response was better in the 16 Gy group in the study by Nguyen *et al.* because the lesions were smaller than the 12 Gy group (≤4 versus >4 cm) (12). However, the reason why the study by Pielkenrood *et al.* was negative is still unknown because the SBRT dose used was even higher (BED10 50.4 to 60 Gy in Pielkenrood *et al.* versus 26.4 to 41.6 Gy in Nguyen *et al.*) (12,14). As for spine SBRT, further studies are needed to determine the timing of pain flare and limiting radiation dose for radiation-related fractures. Studies also are needed to determine indications for when surgical stabilization of non-spine bones should be performed to reduce risks of radiation-induced fractures.

The publication of Sahgal *et al.* triggered different opinions in the radiation oncology community on whether to adopt its results for patients with painful spine metastases. Cellini *et al.* suggested that only selected patients should be offered SBRT since there are still many unanswered questions about the technique, such as the optimal dose and the need for a simultaneous integrated boost (53). In response, Sahgal *et al.* advocated for SBRT as the standard of care and that that future studies should focus on improving SBRT technique instead of comparing the efficacy of SBRT and cEBRT (54). van der Velden *et al.* concurred with Cellini *et al.* that patients should be carefully selected for SBRT, given that this treatment is more time-consuming and expensive. Their team suggested that patients at least should have an expected long life expectancy before offering the option of SBRT (55).

It would seem reasonable to preferentially offer SBRT

Table 5 Summary of existing knowledge on SBRT versus cEBRT for the treatment of painful bone metastases

What we know
SBRT is more resource- and labour-intensive compared to cEBRT
Treatment time of SBRT is longer than cEBRT
SBRT is more expensive compared to cEBRT
What is possible based on existing evidence
Complete pain response rate is higher in SBRT than cEBRT at 3 and 6 months
Local control is better in SBRT compared to cEBRT
SBRT causes higher rates of pain flare compared to cEBRT
What is uncertain based on existing evidence
Whether overall pain response of SBRT is better than cEBRT
Whether fracture rates are different between SBRT and cEBRT in the long term
Whether quality of life after treatment are different between SBRT and cEBRT
How to define "oligometastatic" state to select the ideal candidate for SBRT
What we do not know and needs further study
Time to onset of pain response after SBRT compared to cEBRT
Durability of pain relief after initial pain response to SBRT compared to cEBRT
Patient preference for the type of radiation treatment
The optimal dose schedule of SBRT
Whether pain response is different in spinal and non-spinal lesions

SBRT, stereotactic body radiation therapy; cEBRT, conventional external beam radiotherapy.

to patients with a longer expected survival. However, estimating the length of survival of patients with bone metastases is very complex, as many factors that come into play. Zeng *et al.* found that less radiosensitive histology, presence of paraspinal disease, Eastern Cooperative Oncology Group (ECOG) score 2 or higher, the presence of polymetastatic disease, and the presence of pain were independent prognostic factors for survival of fewer than 3 months in patients treated with spinal SBRT (56). Jensen *et al.* developed a Prognostic Index for Spine Metastases (PRISM) based on patients treated with spinal SBRT in clinical trials. Factors in the scoring system included gender, performance status, previous therapy at the intended treatment site, number of organ systems involved, the time elapsed between diagnosis and metastasis, and number of

spine metastases (57). This scoring system was validated with a retrospective cohort but has not been used to stratify patients in clinical trials. Further prospective validation studies of relevant prognostic factors and prognostic indices for patients with both spine and non-spine bone metastases are warranted to support their use in the clinic.

The use of SBRT for painful bone metastases may be most justified in the oligometastatic setting (58), especially if resources are limited. Local control can be maximised with SBRT, which may in turn translate into improved overall survival (59). Prospective studies are needed to confirm the survival, pain control and QOL benefits of SBRT in different patterns of oligometastatic bone disease.

The above questions may warrant several prospective trials to answer, which will take several years to perform. A meta-analysis of individual participant data from existing randomised controlled trials would be helpful in providing some preliminary data to guide treatment decisions in the interim. Firstly, this allows for reassessing patients' pain responses based on a common set of definitions. Secondly, patients can be regrouped based on the SINS and Mirels' scores for spine and long bone lesions, respectively. Those who have an unstable spine or impending fractures can be included in a sensitivity analysis. Prognostic factors for pain outcomes, such as the number of spine lesions and size of soft tissue mass, can be studied with a larger patient number as well. In addition, separate analyses can be performed in patients with spine and non-spine bone metastases, and patients with radioresistant and radiosensitive histologies. We encourage Ryu *et al.* to publish their full results to allow researchers to better understand why a benefit was not observed in their SBRT arm. When individual patients treated with different SBRT dose schedules are pooled together, we may be able to show a clearer relationship between radiation dose and pain response. A dose threshold above which further escalation would result in deleterious effects on pain control or toxicities may also be defined.

Conclusions

Based on the systematic reviews on RCTs published to date, SBRT may produce a better complete pain response at 3 and 6 months compared to cEBRT in painful bone metastases. However, the effect on overall pain response, especially at earlier time points, is uncertain. Future studies need to focus on selecting the optimal candidate and dose schedule for SBRT. *Table 5* summarizes our current understanding of SBRT for the treatment of painful bone metastases and

areas where further research should focus on. While we await the results of prospective studies, the international community should consider developing consensus guidelines with a Delphi study to guide SBRT use. Routine use of SBRT for all patients with painful bone metastases, however, may postpone effective pain treatment in patients with poor prognoses and put added strain on healthcare systems.

Acknowledgments

Footnote

Provenance and Peer Review: This article was commissioned by the Editorial Office, *Annals of Palliative Medicine* for the series "Palliative Radiotherapy Column". The article has undergone external peer review.

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-23-218/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-23-218/coif). The series "Palliative Radiotherapy Column" was commissioned by the editorial office without any funding or sponsorship. C.B.S. serves as the co-Editor-in-Chief of *Annals of Palliative Medicine*. C.J. serves as the unpaid co-chair for the Palliative Radiotherapy Subcommittee of *Annals of Palliative Medicine* from February 2022 to January 2024 and served as the unpaid Guest Editor of the series. Q.N.N. serves as the unpaid member of Palliative Radiotherapy Subcommittee of *Annals of Palliative Medicine* from February 2022 to January 2024. E.C. serves as the unpaid co-chair for the Palliative Radiotherapy Subcommittee and unpaid Editorial Board Member of *Annals of Palliative Medicine* from February 2022 to January 2024 and served as the unpaid Guest Editor of the series. E.O. serves as the unpaid member of Palliative Radiotherapy Subcommittee of *Annals of Palliative Medicine* from December 2022 to November 2024. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Macedo F, Ladeira K, Pinho F, et al. Bone Metastases: An Overview. Oncol Rev 2017;11:321.
2. Tsukamoto S, Kido A, Tanaka Y, et al. Current Overview of Treatment for Metastatic Bone Disease. Curr Oncol 2021;28:3347-72.
3. von Moos R, Costa L, Ripamonti CI, et al. Improving quality of life in patients with advanced cancer: Targeting metastatic bone pain. Eur J Cancer 2017;71:80-94.
4. De Felice F, Piccioli A, Musio D, et al. The role of radiation therapy in bone metastases management. Oncotarget 2017;8:25691-9.
5. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007;25:1423-36.
6. Behroozian T, Navarro I, Hoskin P, et al. Update on the systematic review/meta-analysis of uncomplicated bone metastases treated with external beam radiation. Radiother Oncol 2022;174:109-10.
7. Imano N, Saito T, Hoskin P, et al. Pain Response Rates After Conventional Radiation Therapy for Bone Metastases Assessed Using International Consensus Pain Response Endpoints: A Systematic Review and Meta-Analysis of Initial Radiation Therapy and Reirradiation. Int J Radiat Oncol Biol Phys 2023;S0360-3016(23)00099-8.
8. Tseng CL, Eppinga W, Charest-Morin R, et al. Spine Stereotactic Body Radiotherapy: Indications, Outcomes, and Points of Caution. Global Spine J 2017;7:179-97.
9. Berwouts D, De Wolf K, Lambert B, et al. Biological 18[F]-FDG-PET image-guided dose painting by numbers for painful uncomplicated bone metastases: A 3-arm randomized phase II trial. Radiother Oncol 2015;115:272-8.

10. Sprave T, Verma V, Förster R, et al. Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy. Radiother Oncol 2018;128:274-82.

11. Sahgal A, Myrehaug SD, Siva S, et al. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. Lancet Oncol 2021;22:1023-33.

12. Nguyen QN, Chun SG, Chow E, et al. Single-Fraction Stereotactic vs Conventional Multifraction Radiotherapy for Pain Relief in Patients With Predominantly Nonspine Bone Metastases: A Randomized Phase 2 Trial. JAMA Oncol 2019;5:872-8. Erratum in: JAMA Oncol 2021;7:1581.

13. Ryu S, Deshmukh S, Timmerman RD, et al. Radiosurgery Compared To External Beam Radiotherapy for Localized Spine Metastasis: Phase III Results of NRG Oncology/RTOG 0631. Int J Radiat Oncol Biol Phys 2019;105:S2-3.

14. Pielkenrood BJ, van der Velden JM, van der Linden YM, et al. Pain Response After Stereotactic Body Radiation Therapy Versus Conventional Radiation Therapy in Patients With Bone Metastases-A Phase 2 Randomized Controlled Trial Within a Prospective Cohort. Int J Radiat Oncol Biol Phys 2021;110:358-67.

15. Sakr A, Hashem WB, Ebrahim N, et al. Randomized Pilot Study of 20 Gy in 5 Fractions versus 27 Gy in 3 Fractions Radiotherapy for Treating Painful Bone Metastases: A Single Institution Experience. Asian Pac J Cancer Prev 2020;21:1807-11.

16. Lutz S, Balboni T, Jones J, et al. Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline. Pract Radiat Oncol 2017;7:4-12.

17. van der Velden J, Willmann J, Spałek M, et al. ESTRO ACROP guidelines for external beam radiotherapy of patients with uncomplicated bone metastases. Radiother Oncol 2022;173:197-206.

18. Song X, Wei J, Sun R, et al. Stereotactic Body Radiation Therapy Versus Conventional Radiation Therapy in Pain Relief for Bone Metastases: A Systematic Review and Meta-Analysis. Int J Radiat Oncol Biol Phys 2023;115:909-21.

19. Ito K, Saito T, Nakamura N, et al. Stereotactic body radiotherapy versus conventional radiotherapy for painful bone metastases: a systematic review and meta-analysis of randomised controlled trials. Radiat Oncol 2022;17:156.

20. Wang Z, Li L, Yang X, et al. Efficacy and safety of stereotactic body radiotherapy for painful bone metastases: Evidence from randomized controlled trials. Front Oncol 2022;12:979201.

21. Lee CC, Soon YY, Cheo T, et al. Stereotactic body radiation therapy versus conventional external beam radiation therapy for painful bone metastases: A systematic review and meta-analysis of randomized trials. Crit Rev Oncol Hematol 2022;178:103775.

22. Akobeng AK. Understanding systematic reviews and meta-analysis. Arch Dis Child 2005;90:845-8.

23. International bone metastases consensus on endpoint measurements for future clinical trials: proceedings of the first survey and meeting (work in progress) International Bone Metastases Consensus Working Party. Clin Oncol (R Coll Radiol) 2001;13:82-4.

24. Chow E, Hoskin P, Mitera G, et al. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. Int J Radiat Oncol Biol Phys 2012;82:1730-7.

25. Ryu S, Pugh SL, Gerszten PC, et al. RTOG 0631 phase 2/3 study of image guided stereotactic radiosurgery for localized (1-3) spine metastases: phase 2 results. Pract Radiat Oncol 2014;4:76-81.

26. Fisher CG, DiPaola CP, Ryken TC, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine (Phila Pa 1976) 2010;35:E1221-9.

27. Fisher CG, Schouten R, Versteeg AL, et al. Reliability of the Spinal Instability Neoplastic Score (SINS) among radiation oncologists: an assessment of instability secondary to spinal metastases. Radiat Oncol 2014;9:69.

28. Fox S, Spiess M, Hnenny L, et al. Spinal Instability Neoplastic Score (SINS): Reliability Among Spine Fellows and Resident Physicians in Orthopedic Surgery and Neurosurgery. Global Spine J 2017;7:744-8.

29. Saito T, Murotani K, Ito K, et al. Bias due to statistical handling of death and reirradiation in the assessment of duration of response after palliative radiotherapy: a scoping review and analysis of clinical data. Br J Radiol 2023;96:20220398.

30. Spencer K, Velikova G, Henry A, et al. Net Pain Relief After Palliative Radiation Therapy for Painful Bone Metastases: A Useful Measure to Reflect Response Duration? A Further Analysis of the Dutch Bone Metastasis Study. Int J Radiat Oncol Biol Phys 2019;105:559-66.

31. Amini A, Shinde A, Wong J. Palliative Radiation for Cancer Pain Management. Cancer Treat Res 2021;182:145-56.

32. Sohn S, Chung CK, Sohn MJ, et al. Radiosurgery Compared with External Radiation Therapy as a Primary Treatment in Spine Metastasis from Hepatocellular Carcinoma : A Multicenter, Matched-Pair Study. J Korean Neurosurg Soc 2016;59:37-43.

33. Sohn S, Chung CK, Sohn MJ, et al. Stereotactic radiosurgery compared with external radiation therapy as a primary treatment in spine metastasis from renal cell carcinoma: a multicenter, matched-pair study. J Neurooncol 2014;119:121-8.

34. van de Ven S, van den Bongard D, Pielkenrood B, et al. Patient-Reported Outcomes of Oligometastatic Patients After Conventional or Stereotactic Radiation Therapy to Bone Metastases: An Analysis of the PRESENT Cohort. Int J Radiat Oncol Biol Phys 2020;107:39-47.

35. Zeng KL, Myrehaug S, Soliman H, et al. Mature Local Control and Reirradiation Rates Comparing Spine Stereotactic Body Radiation Therapy With Conventional Palliative External Beam Radiation Therapy. Int J Radiat Oncol Biol Phys 2022;114:293-300.

36. Westhoff PG, de Graeff A, Monninkhof EM, et al. Quality of Life in Relation to Pain Response to Radiation Therapy for Painful Bone Metastases. Int J Radiat Oncol Biol Phys 2015;93:694-701.

37. Niv D, Kreitler S. Pain and quality of life. Pain Pract 2001;1:150-61.

38. Rustøen T, Moum T, Padilla G, et al. Predictors of quality of life in oncology outpatients with pain from bone metastasis. J Pain Symptom Manage 2005;30:234-42.

39. Pielkenrood B, Van der Velden J, Van der Linden Y, et al. OC-0372: Phase 2 RCT comparing conventional radiotherapy with SBRT in patients with bone metastases. Radiother Oncol 2020;152:abstr S201-2.

40. Wong P, Lambert L, Thanomsack P, et al. Quality of Life: A Prospective Randomized Trial of Palliative Volumetric Arc Therapy Versus 3-Dimensional Conventional Radiation Therapy. Int J Radiat Oncol Biol Phys 2021;109:1431-9.

41. Sprave T, Verma V, Förster R, et al. Quality of Life and Radiation-induced Late Toxicity Following Intensity-modulated Versus Three-dimensional Conformal Radiotherapy for Patients with Spinal Bone Metastases: Results of a Randomized Trial. Anticancer Res 2018;38:4953-60.

42. Olson R, Schlijper R, Chng N, et al. SUPR-3D: A randomized phase iii trial comparing simple unplanned palliative radiotherapy versus 3d conformal radiotherapy for patients with bone metastases: study protocol. BMC Cancer 2019;19:1011.

43. Cassidy V, Amdur RJ. Esophageal Damage From Thoracic Spine Stereotactic Body Radiation Therapy. Pract Radiat Oncol 2022;12:392-6.

44. Kowalchuk RO, Brown PD, Merrell KW. In reply to Cassidy and Amdur. Pract Radiat Oncol 2022;12:e460-2.

45. Kowalchuk RO, Mullikin TC, Kim DK, et al. Cost-Effectiveness of Treatment Strategies for Spinal Metastases. Pract Radiat Oncol 2022;12:236-44.

46. Donaldson C, Currie G, Mitton C. Cost effectiveness analysis in health care: contraindications. BMJ 2002;325:891-4.

47. Vancak V, Goldberg Y, Levine SZ. Guidelines to understand and compute the number needed to treat. Evid Based Ment Health 2021;24:131-6.

48. Arifin AJ, Young S, Sahgal A, et al. Planning for the Impact of SC.24 on Spine Stereotactic Body Radiotherapy (SBRT) Utilization at a Tertiary Cancer Center. Int J Radiat Oncol Biol Phys 2022;114:e86.

49. Banta HD, de Wit GA. Public health services and cost-effectiveness analysis. Annu Rev Public Health 2008;29:383-97.

50. Marseille E, Larson B, Kazi DS, et al. Thresholds for the cost-effectiveness of interventions: alternative approaches. Bull World Health Organ 2015;93:118-24.

51. Zeng KL, Abugarib A, Soliman H, et al. Dose-Escalated 2-Fraction Spine Stereotactic Body Radiation Therapy: 28 Gy Versus 24 Gy in 2 Daily Fractions. Int J Radiat Oncol Biol Phys 2023;115:686-95.

52. Simone CB 2nd. Stereotactic body radiation therapy versus multi-fraction radiation therapy for bone metastases. Ann Palliat Med 2019;8:360-3.

53. Cellini F, Manfrida S, Gambacorta MA, et al. Stereotactic body radiotherapy for painful spinal metastases. Lancet Oncol 2021;22:e384.

54. Sahgal A, Brundage M, Ding K, et al. Stereotactic body radiotherapy for painful spinal metastases - Authors' reply. Lancet Oncol 2021;22:e385.

55. van der Velden JM, van der Linden YM. Spinal stereotactic radiotherapy for painful spinal metastasis. Lancet Oncol 2021;22:901-3.

56. Zeng KL, Sahgal A, Tseng CL, et al. Prognostic Factors Associated With Surviving Less Than 3 Months vs Greater Than 3 Years Specific to Spine Stereotactic Body Radiotherapy and Late Adverse Events. Neurosurgery

2021;88:971-9.

57. Jensen G, Tang C, Hess KR, et al. Internal validation of the prognostic index for spine metastasis (PRISM) for stratifying survival in patients treated with spinal stereotactic radiosurgery. J Radiosurg SBRT 2017;5:25-34.

58. Milano MT, Biswas T, Simone CB 2nd, et al.

Oligometastases: history of a hypothesis. Ann Palliat Med 2021;10:5923-30.

59. Rim CH, Shin IS, Park S, et al. Benefits of local consolidative treatment in oligometastases of solid cancers: a stepwise-hierarchical pooled analysis and systematic review. NPJ Precis Oncol 2021;5:2.