Spinal stereotactic radiotherapy for painful spinal metastasis

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I declare no competing interests.

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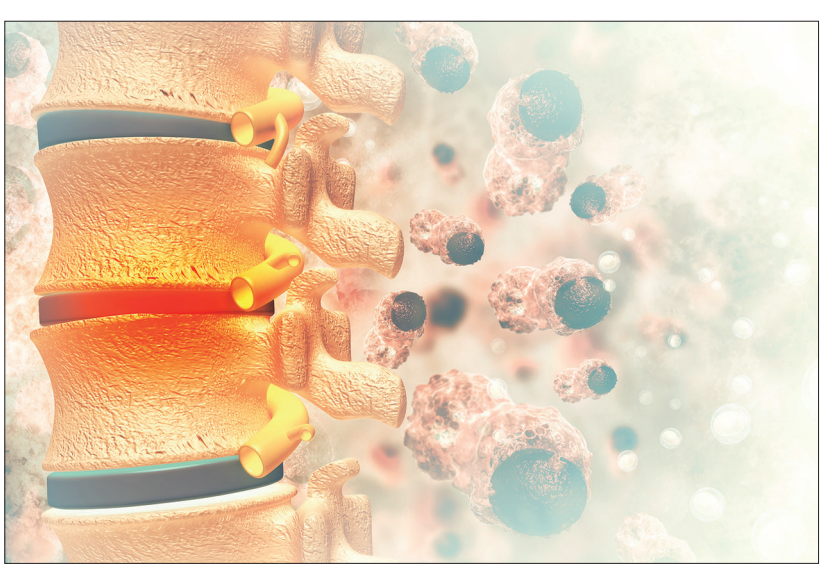
Conventional external beam radiotherapy is the standard of care for patients with cancer who have localised metastatic bone pain. Pain response is reported as a combination of complete (defined as a pain score of 0 on an 11-point scale of 0–10) and partial (defined as a reduction of ≥2 points, without an increase in analgesic consumption) responses, in accordance with the International Consensus Pain Response Endpoints to promote consistent reporting in clinical trials.[1] Pooled data from almost 30 randomised trials show that 65% of patients treated with conventional external beam radiotherapy had an overall response for pain (ie, a partial or complete response) and 25% had a complete response for pain.[2] This review[2] also showed that dose escalation with multiple fractions of conventional external beam radiotherapy did not increase the complete response rate for pain. Therefore, a dose of 8 Gy in a single fraction is considered the gold standard for treating painful bone metastases. With the aim of further improving response rates for pain, stereotactic body radiotherapy, which enables the delivery of high doses of radiation with high precision, has been studied over the past 15 years in patients with bone metastases.

In *The Lancet Oncology*, Arjun Sahgal and colleagues[3] report the findings of an open-label, multicentre, randomised, controlled, phase 2/3 trial comparing pain responses in patients with painful spinal metastases following delivery of conventional external beam radiotherapy at a dose of 20 Gy in five fractions or stereotactic body radiotherapy at a dose of 24 Gy in two fractions. Commendably, the authors completed this randomised controlled trial involving 229 participants in less than 4 years. The results showed that 16 (14%) of 115 patients in the conventional external beam radiotherapy group versus 40 (35%) of 114 patients in the stereotactic body radiotherapy group had a complete response for pain at 3 months (p=0·0002). The authors concluded that their findings support a shift toward the use of stereotactic body radiotherapy for spinal metastases in the palliative setting.



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The trial by Sahgal and colleagues[3] is one of five published randomised trials comparing conventional external beam radiotherapy with stereotactic body radiotherapy in patients with bone metastases. In 2018, Sprave and colleagues[4] claimed that after stereotactic body radiotherapy at a dose of 24 Gy in one fraction, pain scores decreased faster and were lower at 6 months when compared with conventional external beam radiotherapy at a dose of 30 Gy in ten fractions in 55 patients with spinal metastases. This was a remarkable statement, since their primary endpoint of overall pain response at 3 months after treatment was not significantly different between the two radiotherapy groups. Nguyen and colleagues[5] found higher overall response rates for pain at several timepoints (from 2 weeks to 9 months) after stereotactic body radiotherapy (at doses of 12 Gy or 16 Gy in one fraction) than after conventional external beam radiotherapy (at a dose of 30 Gy in ten fractions) in 160 patients with predominantly non-spinal bone metastases. The primary endpoint in this trial[5] was overall response for pain, but the authors did not specify beforehand at which timepoint the primary endpoint was measured. A randomised phase 2 trial by Pielkenrood and colleagues[6] found no differences in complete or partial responses for pain after conventional external beam radiotherapy (delivered with various fractionation schemes, mostly 8 Gy in one fraction) or stereotactic body radiotherapy (delivered with various fractionation schemes, mostly 30 Gy in three fractions). Finally, Ryu and colleagues[7] presented the results of the NRG Oncology/RTOG 0631 trial at the ASTRO 2019 meeting. In this trial, 339 patients were randomly assigned to receive either conventional external beam radiotherapy at a dose of 8 Gy in one fraction or stereotactic body radiotherapy at a dose of 16 Gy or 18 Gy in one fraction; no significant difference in overall response for pain at 3 months after treatment was observed.

At first sight, three of these five randomised studies appear to indicate that stereotactic body radiotherapy is a better treatment option than conventional external beam radiotherapy. However, after aligning the results of these trials, and looking at the overall response rates for pain in the intention-to-treat population at 3 months, four trials[4-7] did not find a significant difference between conventional external beam radiotherapy and stereotactic body radiotherapy.

Importantly, although Sahgal and colleagues[3] report the proportion of patients who had a partial response for pain after conventional external beam radiotherapy (29 [25%] of 115 patients) and stereotactic body radiotherapy (20 [18%] of 114) at 3 months, they did not statistically compare the two groups. Moreover, the overall response rate for pain was not included as a secondary or tertiary endpoint. As a decrease in pain score of 2 points is already considered as clinically relevant to patients with painful lesions,[8] a combined endpoint of complete and partial responses for pain would be more clinically relevant than a complete response for pain alone. Reporting on both complete and partial responses for pain would improve comparability with other trials, which is important for inclusion in a systematic review. For the radiotherapy community to agree on the best stereotactic body radiotherapy fractionation schedule, comparable results are needed. Furthermore, Sahgal and colleagues[3] report the complete response rate for pain at 1, 3, and 6 months after treatment. Unfortunately, they were not able to report the duration of response for pain in patients specifically. This outcome is important for patients, since radiotherapy is not only about reducing pain, but also about showing that this effect is durable.

The five randomised trials[3-7] differ in terms of size of study population and location of bone metastases. Spinal metastases are similar to non-spine bone metastases in terms of bone involvement and pain relief after standard radiotherapy;[9] therefore, the different location of bone metastases does not explain the different results between the trial by Sahgal and colleagues[3] and the other trials.[4-7] In addition, the studies were similar in terms of primary tumour site (most patients had lung cancer in four of the trials,[3-6] whereas the most frequent primary tumour site was unknown in the NRG Oncology/RTOG 0631 trial), performance status (most patients had an Eastern Cooperative Oncology Group score of 1 or a Karnofsky performance score of 70–80), and baseline pain score (numeric rating score of 6–7), which are known factors associated with response for pain after radiotherapy.[10] An important difference among these studies, however, is the stereotactic body radiotherapy dose fractionation schedule. Most trials delivered the stereotactic body radiotherapy dose in one fraction,[4,5,7] or in mostly three or five fractions,[6] whereas the dose in the trial by Sahgal and colleagues[3] was delivered in two fractions. It is possible that Sahgal and colleagues[3] chose the appropriate

stereotactic body radiotherapy dose regimen with the optimal number of fractions.

Decision making remains complex in this patient population, as randomised trials completed to date do not seem to support the routine use of stereotactic body radiotherapy in patients with bone metastases. However, it is possible that a subgroup of patients with bone metastases might benefit from this type of radiotherapy. As stereotactic body radiotherapy is a time consuming and a more expensive treatment than conventional external beam radiotherapy that achieves its effect within 3 months after treatment, this strategy should at least be considered in patients with substantial life expectancy. Future efforts should focus on identifying subgroups of patients who are likely to benefit from stereotactic body radiotherapy by improving patient selection, assessing duration of response for pain, and finding, or verifying, the optimal stereotactic body radiotherapy dose regimen.

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Immunotherapy in ovarian cancer: we are not there yet

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With the disappointment brought by modest results of trials testing single-agent immune checkpoint inhibitors in recurrent ovarian cancer,[1,2] renewed optimism arose around the possibility that combination treatments would deliver the positive results the community was waiting for. Surely, there would be a way to enhance the activity of immunotherapy in recurrent ovarian cancer, a setting in which progress had remained elusive. In other tumour types, chemotherapy had been shown to induce antigen presentation, priming tumour cells to become receptive to the immune attack triggered by PD-L1 inhibitors and yielding improved clinical outcomes.[3,4] Those data revitalising the field of immunotherapy in solid tumours provided the rationale for also testing immune checkpoint inhibitors with chemotherapy in ovarian cancer.

In *The Lancet Oncology*, Eric Pujade-Lauraine and colleagues[5] describe the results of the JAVELIN-200 trial, an open-label, randomised, phase 3 study of avelumab monotherapy, avelumab plus pegylated liposomal doxorubicin (PLD), and PLD monotherapy in women with platinum-resistant or platinum-refractory ovarian cancer. The primary endpoints were progression-free survival by blinded independent central review and overall survival. Prespecified biomarker analyses included assessment of PD-L1 expression and presence of CD8-positive cells. Overall, the trial did not show improvement in progression-free survival or overall survival with avelumab alone or avelumab plus PLD compared with PLD alone, either in the main analysis or in the predefined PD-L1-positive or CD8-positive subsets. However, in the cohort of patients whose tumours expressed PD-L1 and had CD8-positive cells, a group not prespecified a priori and representing approximately one third of the study population, the unstratified hazard ratios for both progression-free