

For personal use only. Not to be reproduced without permission of the publisher (copyright@ppme.eu).

Bone metastases and treatment by irradiation

The utility and efficacy of radiation therapy in bone metastases has been demonstrated. However, more research is needed to define treatment indicators more precisely and to adapt radiotherapy to changing chemotherapeutic and targeted treatment regimes.

Radiation therapy is one of the most important tools in the treatment of bone metastases. Using the evidence base of modern, recently published clinical trials, it is possible to propose treatment with good scientific evidence. It must be used as part of a global strategy and decisions on its use must be made in multidisciplinary meetings.



A meta-analysis by Wu et al. [1] evaluated all trials of bone irradiation for treatment of metastases. They were amalgamated in three categories

- Single fraction: 4 Gy vs. 8 Gy
- Single fraction versus multiple fractions
- Different modalities of fractionation: 15/20 Gy vs. 24/30 Gy

The primary outcomes of interest were complete and overall pain relief. But the response was analysed according with different clinical criteria: the most important effects were complete response or the global response.

Single fraction 8 Gy dosing seems to have been the most effective but there was no difference in complete response. No difference was demonstrated, in complete response, in the trials comparing single versus multiple fractions (34.4% vs. 32.3% (p = 0.5)). Nevertheless if the global response was considered, giving the radiation as a single dose was more effective (62.1% vs. 58.7%: p = 0.04; RR = 1.05). No dose-response effects were demonstrated when looking at the different schemes, but re-irradiation was more frequent with low doses

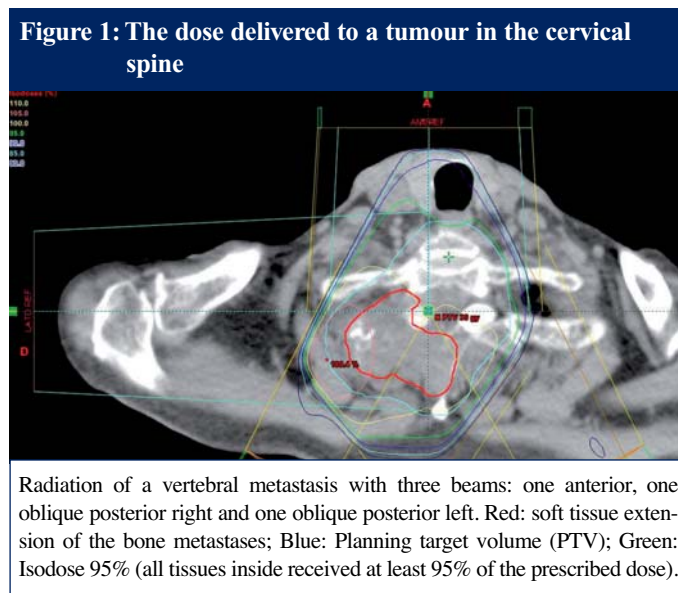
and fractures were more frequent with single doses than with multiple fraction treatments. Finally the length of the response varied from 11 to 24 weeks while the acute tolerance was equivalent in all trials.

With these results in mind, some recommendations can be suggested:

- If the analgesic effect is the principal objective for a single metastasis with no complications, or if there are just a few metastases, the best treatment is treatment in one fraction.
- In the opposite situation, or if the objective is different, the choice can be adapted to the situation. If there is a risk of a fracture, or a significant mass around the bone metastases, or if there is spinal compression, multiple fraction schemes must be used.
- Finally the benefit of highly fractionated doses was not demonstrated even in patients with a good prognosis (see Table 1 and Figure 1).

The results of the recently published RTOG 97-14 trial [2] demonstrated that, at three months, there is an equivalence in period of response between 8 Gy/1 fraction (arm A) and 30 Gy/10 fractions (arm B). Eight hundred and ninety-eight patients were randomised, 288 were analysed in arm A and 285 in arm B. The median survival was 9.1 vs. 9.5 months; the acute tolerance (grade 2 and 3) was 10% vs. 17% (p 0.002). The late tolerance (grade 2 and 3) was equivalent in the two arms. The risk of fracture was 5% vs. 4% and from the opposite

Reasons to choose multiple fraction irradiation	Reasons to choose monofraction irradiation
Minimises the risk of painful relapse	Evidence: more effective No survival difference against pain
Minimises the risk of spinal compression	Choice of the patient
Minimises the number of re-irradiation sessions	Well-educated physician
A common practice	Low performance status
Less burden on long bones	Small number of treatments
First metastases	Patient lives at a distance
Less dangerous for the spinal cord, brain	Workflow of the department
Young (age <40 yrs)	Older patients
Lytic metastasis	



perspective re-irradiation was more frequent in arm A (18% vs. 9%, $p < 0.01$). Only patients with breast and prostate cancer were included in this trial. The pain was evaluated only in 573 patients at three months and 160 patients had died or were too tired to answer the questionnaire.

Van der Linden et al. [3] analysed the patients who survived one year after inclusion in a prospective trial which evaluated irradiation with one fraction versus 24 Gy in six fractions, 1,157 patients were included; 320 patients survived. In 63% of patients the primary tumour was breast cancer, 24% prostate

Recent trials with sufficient power have shown equivalence between irradiation in one fraction and irradiation in five to six fractions.

cancer, 8% lung cancer and 5% different localisations. In the one fraction arm 163 patients were alive vs. 157. A global response to pain was obtained in 87% vs. 85%, which was complete in 62% vs. 48% of subjects. The median survival was 35 and 42 weeks respectively. No difference could be shown in the evolution of the pain during the first year, nor did the differing histology of the primary tumour appear to correlate with the effectiveness of the treatment. The analysis of survival in the 1,157 patients showed that the survival differed significantly for breast cancer, prostate cancer and the other tumours or lung cancer. Fifty percent of the patients were alive at 18, 12 and six months, respectively.

Several prognostic factors were demonstrated regarding the efficacy of the treatment. These factors were Karnofsky score >80 , the number of bone metastases (single or multiple), visceral metastases, treatment with morphine, pain score 8–10 on the EVA scale and finally systemic treatment. (The Karnofsky index gives clinical estimate of a patient's physical state, performance, and prognosis after a therapeutic procedure on a scale 0–100. EVA equates maximum pain to 10.)

Finally, recent trials with sufficient power have shown equivalence between irradiation in one fraction and irradiation in five to six fractions. But in practice, what can be offered to the patient? How does practice vary in different countries and finally what do patients choose? Lievens et al. studied practice in different countries and institutions classified according to the number of patients treated per year [4]. Treatment in multiple fractions is generally used in Canada, Europe, New Zealand and USA. Within this there is a large heterogeneity of practices. These justify the therapeutic choices presented in Table 1.

Patient preferences were evaluated by Shakespeare et al. [5]. After being informed of the advantages and the risks of two strategies (8 Gy/1 fraction and 24 Gy in six fractions), 62 patients were included. Eighty-five percent of the population chose the fractionated treatment. Their reasons for this were firstly the risk of re-irradiation and secondly bone fracture.

The other 15% of patients based their choice on the cost and the convenience of only one treatment. No objective criteria were found to distinguish the two groups. But 84% of patients were very positive about being involved in the treatment decision.

Conclusion

Treatment of bone metastases is an important option but is frequently used belatedly. In the light of modern trials, it should be considered earlier, as active treatment, but trials have not yet been large enough to give firm indications of treatment

options. The populations included in these trials are usually a mixture of patients with metastases from breast, prostate and lung cancer. Only in one trial did the population consist of patients with metastases solely from breast tumours [6]. The impact of new medical treatments such as bisphosphonates has also not yet been evaluated in published trials. Finally, I would like to call for trials of irradiation associated with new drugs and trials of metabolic irradiation.

Author

Professor Jean-Leon Lagrange, MD
Department Radiation Oncology
APHP Henri-Mondor Hospital, Paris 12 University
F-94000 Créteil, France
Lagrange.jeanleon@gmail.com

References

1. Wu JS, Wong R, Johnston M, et al. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys.* 2003; 55(3):594-605.
2. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst.* 2005;97 (11):798-804.
3. Van der Linden YM, Steenland E, van Houwelingen HC, et al. Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study. *Radiother Oncol.* 2006;78(3):245-53.
4. Lievens Y, Kesteloot K, Rijnders A, et al. Differences in palliative radiotherapy for bone metastases within Western European countries. *Radiother Oncol.* 2000;56(3):297-303.
5. Shakespeare TP, Lu JJ, Back MF, et al. Patient preference for radiotherapy fractionation schedule in the palliation of painful bone metastases. *J Clin Oncol.* 2003;21(11):2156-62.
6. Rasmusson B, Vejborg I, Jensen AB, et al. Irradiation of bone metastases in breast cancer patients: a randomized study with 1 year follow-up. *Radiother Oncol.* 1995;34 (3):179-84.