

Radiotherapy in palliative treatment of metastatic NSCLC: not all one and the same

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This is not the first editorial on palliative radiotherapy in metastatic NSCLC. Moreover, this is not the first editorial which underlines the relationship between radiotherapy dose/fractionation and patient prognosis. So, why another one? And why another one now?

The role of an editorial is to incorporate the results of a new relevant study in the scientific scenario, shedding light on some particular results of the trial which can change the clinical practice. In the January issue of *Journal of Clinical Oncology* Chen *et al.* (1), palliative RT dose and fractionation in a large national population-based cohort of patients with metastatic NSCLC was investigated. Out of 1,574 patients, 780 (50%) received at least one course of RT and 21% and 12% received RT to the chest and bone, respectively. Among patients receiving palliative bone RT, only 6% received single-fraction treatment. Among patients receiving palliative chest RT, 42% received more than 20 fractions. The author's conclusion was that when palliative RT is used in patients with metastatic NSCLC, a substantial proportion of patients receive a greater number of treatments and higher doses than supported by current evidence, suggesting an opportunity to improve care delivery.

As previously stated, the argument is not new, certainly. On one hand, recent years have shown the publication of many phase III trials (2-5), systematic reviews (6,7) and guidelines (8,9) which have confirmed that various shorter external beam radiotherapy dose/fractionation schedules provide good symptomatic relief for bone metastasis and for chest symptoms. On the other hand, national and international practice surveys (10,11), as well as several editorials (12,13), have pointed out the reluctance of radiation oncologists for short prescriptions. As Bogart (12)

stated, "*the pen starts to quiver when writing a prescription for the extreme hypofractionation*". Fairchild *et al.* (14) have published an analysis of prescription patterns at the Rapid Response Radiotherapy Program trying to determine whether or not the publication of data made a difference in physician prescriptions. They reported that level I evidence had failed to bring about major changes in their behaviour. The reluctance to change established patterns of practice is not well studied and there are probably multiple determinants, but as some authors suggest (13), it may include elements of habit, lack of knowledge of recent clinical data or, in some cases, economic advantages of established fractionations regimes.

This editorial's perspective is broader. It aims to restore the dignity of the radiation oncologist's thought-process, by showing that the thinking captures the nuances of the specific clinical situation, which no other phase III study has done thus far. Obviously, evidence-based medicine is the cornerstone of scientific progress, but as already shown, it can sometimes lead to an overly simplistic solution. It is well known that patients with metastatic disease can have a broad spectrum of presentation and a subsequent varied prognosis. In recent years, the concept of oligometastatic disease has been introduced.

The term "oligometastases" was first described by Hellman and Weichselbaum in 1995 (15) as "... a less advanced state of metastatic disease amenable to and potentially curable with local therapy". A significant phrase of Milano (16) alludes to the same: "the notion of metastatic disease existing along a disease spectrum is not an hypothesis but merely an observation". In fact, we all have experience of metastatic patients with longer survival than expected. Several studies from surgeons have reported

that surgical resection of metastases prolongs survival in selected patients (17), even if the benefits of resection and appropriate selection criteria in patients who develop metastasis are still poorly defined (18). Today, the question of whether the oligometastatic state truly exists seems to be outdated (19). In fact, pathophysiologic mechanisms of oligometastatic disease have also been identified and reported (20).

It is well known that lung cancer is predisposed to metastasize to the brain, lungs, adrenal glands, bone and liver, while a metastasis to a structure such as the bladder, pancreas or colon is rare. This predisposition is dependent on both the genomic nature of cancer, the seed and the microenvironment, the soil (capacity for vascular adhesion, level of hypoxia), at that site. Distant metastasis occurs late during the genetic evolution of cancer: “founder” mutations and “progressor” mutations “ordered hierarchy establishing an evolutionary path for tumour progression” (21).

Clinical experiences which confirm the existence of the oligometastatic state have been recently reported. The University of Chicago investigated the pattern of failure in patients with stage IIIB-IV NSCLC treated with chemotherapy. Of these, 50% had stable or progressive disease in initially involved sites without development of new metastatic lesions (22). At the University of Colorado, the pattern of failure in patients with stage IIIB-IV NSCLC treated with chemotherapy was local in 68%, distant in 14% and mixed in 18% (23). Cheruvu P. *et al.* made a comparison of the outcomes in patients with stage III versus limited stage IV NSCLC and noted that there were no differences. In the conclusion they suggest that a subset of patients from NSCLC may benefit from a combination of systemic therapy and local aggressive therapy (24). Last year, De Ruyscher reported a prospective phase II trial in which radical treatment of NSCLC patients with synchronous oligometastases was performed (25). This trial investigated whether it would be possible to obtain a significant 2 and 3 years survival in these patients when treated radically with surgery or radiotherapy. The location of metastasis was as follows: brain 44%, bone 18%, adrenal gland 10% and other 28%. The overall survival was 13.5 m, 1 year survival 56% and 2 years survival 23%. The particular observation was that only 5.1% have an in-field recurrence, and that 15% of patients did not show any recurrence at 2 years. Systemic therapy remains the standard of care for patients with metastatic disease, but patients presenting with a limited number and extend of metastatic disease may benefit from localized therapy. Obviously, technologic

advances in radiotherapy have resulted in a greater comfort level in treating patients with oligometastatic disease because of lower treatment-related toxicity. Referring back to the Chen *et al.* report (1), it seems to be a shared view that short course radiotherapy is a safe and effective tool for palliating lung cancer symptoms and it is appropriate for selected poor-prognosis patients. However, it is important to note that the suggestion of improved long-term survival for favourable-risk patients treated with higher radiation doses illustrates the critical need to appropriately classify metastatic NSCLC patients. The challenge for the next decade will be to select those patients who may benefit from more aggressive treatment in a more appropriate manner.

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