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SHORT COMMUNICATION

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# Scoring the effect of radiotherapy for painful bone metastases

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**Abstract** *Rationale:* The evaluation of the analgesic effects of radiotherapy in painful bone metastases is a matter of controversies due to a lack of appropriate tools to define the outcome. An integration of competences in monitoring the pain response and modifying the opioid treatment according to changes of the clinical condition is mandatory. *Proposed method:* A meaningful score, used in previous works to monitor the global response to an analgesic intervention in advanced cancer patients, is proposed. A case report, in which opioids are first titrated and then tapered, is described as an example of application of this method.

**Keywords** Cancer pain · Radiotherapy · Opioids · Monitoring of opioid response

Radiotherapy for painful bone metastases is not an easy topic. About one-fifth of all radiotherapy treatments are performed for painful bone metastases. The outcomes in this field, however, have been poorly assessed. Adequacy of end points used to record data in clinical trials to assess the effectiveness of different fractionation schedules for palliation of bone metastases has been found to be of little value [2]. From meta-analysis, over 40% of patients can expect at least 50% pain relief, and fewer than 30% can expect complete pain relief at 1 month [6]. These data were recently confirmed by a meta-analysis comparing dose-fractionation radiotherapy trials, showing no differences in complete and overall pain relief between single and multifraction radiotherapy [13]. The major methodological issue raised was the definition of pain response. Consensus exists supporting the approach of integrating pain relief with analgesic consumption, that is, response is defined as pain relief without an increase in analgesic consumption [1].

This approach will likely lower the response estimates for any given dose schedule because criteria are more stringent. On the other hand, new pains from symptomatic metastases outside of the irradiated area may contribute to opioid dosage increase and may confound the interpretation of data.

An integration of competences in monitoring the pain response and modifying the opioid treatment according to changes of the clinical condition is mandatory. Moreover, the use of an integrated index may account for overcoming the weakness of most studies assessing the effectiveness of radiotherapy for painful bone metastases. We propose a meaningful score in this context, used in previous works to monitor the global response to an analgesic intervention in advanced cancer patients. As an example of the application of this method, we describe a case of rapid opioid titration in a patient on whom radiotherapy for pain was not performed. After successful radiotherapy, the inverse process allowed to taper the opioid dose in time.

## Case report

A 56-year-old male patient was scheduled for a course of radiotherapy on painful bone metastases from lung cancer. Due to severe pain intensity, he was admitted at the radiotherapy ward, rather than performing the treatment as an outpatient. However, he was unable to collaborate even for radiotherapic simulation, as pain impeded any movement in bed. A pain consultation was required. He presented a severe basal pain (scored as 8 on a numerical scale from 0 to10) and excruciating pain on movement, which impeded any maneuver and was caused by extensive vertebral metastases. The pain impeded all the procedures required for performing radiotherapy. No other distant metastases had been found. He had received tramadol, ketorolac, and dexamethasone, unsuccessfully. Intravenous morphine was titrated with repeated boluses, according to a previously reported protocol [8]. The effective intravenous morphine dose was 8 mg. No adverse effects were recorded. He was started with an intravenous morphine infusion of 60 mg/day. Doses were increased in the next days up to 120 mg/day, and doses as needed were offered to facilitate movements, according to department policy [9]. Three days after, the patient could actively collaborate, and radiotherapy was started when globally receiving 150 mg/day of intravenous morphine. Six days after starting radiotherapy, intravenous morphine was reduced to 45 mg/day due to well-controlled pain and the occurrence of somnolence and confusion (blurred visions). These signs were interpreted as relative overdosing due to reduction of pain intensity. Laboratory test results were normal. Morphine dose was slowly tapered according to the pain intensity and then stopped to maintain a dose of 3 mg intravenously, as needed. During the admission, he also received chemotherapy, including carboplatin, to be discharged on the 16th day after starting radiotherapy and to be continued as an outpatient. At that time the patient had an analgesic prescription of ketorolac 30 mg, to be administered subcutaneously as needed. The patient was assessed continuously during the course and at weekly intervals after discharge, recording routine parameters by using standard scales for pain intensity (numerical scale 0–10), and symptoms (Likaert scale from 0 to 3). Two months after, the patient was receiving nimesulide with good pain control. Effective analgesic score (EAS) was calculated before starting radiotherapy and at fixed weekly intervals on the basis of the following formula: $PI(1+M/10)$ , where 1 indicates administration of anti-inflammatory drugs at fixed times and at full dosage, M indicates the dosage (milligrams) of oral morphine equivalents, and PI indicates the pain intensity on a numerical scale 0–10. This score monitors the analgesic consumption/pain intensity ratio. A slow increase of this score indicates minor problems in achieving adequate analgesia. Of course, a decrease of this score maintained in time means that the active treatment, in this case radiotherapy, was successful. The meaning of this score has been discussed in previous studies [7]. Before starting radiotherapy, EAS was 3×45=135 (intravenous morphine converted to oral morphine was 450 mg). One week after, EAS was 2×13.5=27. Two weeks after, EAS was 2×1=2. Two months after, EAS was 3×1=3. However, 3 months after, the patient was receiving 90 mg of oral morphine to maintain adequate pain control (PI=3/10), as EAS was 27. This means that the effect of radiotherapy had a significant duration of more then 2 months and then declined in time and/or other causes of pain developed. Thus, in this patient, EAS was able to detect the clear improvement in pain intensity, as well as the progressive decrease of opioid doses until discontinuation, during the course of radiotherapy and in the follow-up. Similarly, it was also possible to monitor a progressive loss of analgesia requiring increasing doses of opioids to maintain an adequate level of analgesia.

## Discussion

We have used an index to monitor the response to a specific treatment, either pharmacological or interventional procedures. This proved to be effective to quantify with simple numbers to compare for possible statistical analysis the relationship of pain intensity and opioid dose in patients undergoing analgesic procedures, such as celiac plexus block, combined with an analgesic treatment [7]. Any analgesic procedure or nonpharmacological treatment are unlikely to produce definitive or permanent analgesia without recurring to analgesics. Therefore, it is mandatory to take into account at least two variables, such as pain intensity and analgesic consumption, other than an appropriate timing and experience to modulate the treatment according to the patient's clinical conditions. In this case, EAS has been used to measure the effect of a combination of treatments, including opioids, which can be either titrated and tapered according to the different effects and variability in time of radiotherapy, which produces a slow effect, able to reduce further requests of opioids for an unpredictable period of time. Thus, this integrated score may be helpful in quantifying the general clinical effect in time. Analyzing data from a previous report, for example, and using the EAS score, a clear improvement from 21 (7×3) to 8.4 (3.5×2.4) would be evident, although these data are only presumed and simulated because only changes from basal values and not raw data were reported [11]. From a recent report, morphine doses were doubled 1 week after radiotherapy. Assuming that these doses were used for maintaining similar pain intensity, EAS would be 10 before starting radiotherapy (for a pain level of 4/10) and 20 after 1 week. However, doses of morphine (and

probably EAS, if pain control is adequate) remained constant for about 28 weeks. This accounts for some effect of radiotherapy, rather than leading to the authors' conclusion that the treatment was ineffective [5]. As pointed out by other authors [12], pain intensity would have been evaluated to better judge the intervention.

Unfortunately, radiotherapy is often started in patients with significant pain severity and inadequate opioid dosing, probably due to the lack of multidisciplinary approach. In other words, it is quite difficult to quantify the real basal condition, in terms of opioid requirements in relation to the pain intensity, other then producing obvious suffering for patients. In fact, radiotherapy is known to have a delayed and unpredictable analgesic effect. In the case presented, it was possible to monitor a patient appropriately treated before starting radiotherapy, therefore offering a basal condition to monitor in time in the subsequent period. Three months after therapy, there was the need to use medium doses of opioids. However, opioid requirements were fivefold higher before starting therapy, demonstrating a significant tail effect, even after 3 months.

Thus, the opioid-sparing effect of radiotherapy deserves a combined assessment for an appropriate evaluation of any analgesic treatment to really weigh the indications and the benefit.

Identifying criteria of pain response to radiotherapy is a difficult task. Opioid consumption, taken alone, does not seem to be a useful parameter and is influenced by several variables, including inappropriate treatment. On the other hand, pain intensity cannot be considered separately to judge the outcome. Moreover, pain intensity is often physician-rated, rather than rated by the patient [4]. To complicate the interpretation, inevitably sooner or later, other sites of pain may occur.

This case emphasizes the need of a continuing multidisciplinary approach to circumstances in which pain is severe in the first instance, so requiring rapid opioid titration. However, pain also decreases as a consequence of radiation therapy in an unpredictable way, requiring changes in opioid doses, generally tapering, similarly as it happens after neurolytic procedures or when disease progression compromises pain pathway [3, 10]. Thus, EAS could be considered a useful tool in monitoring the analgesic response in patients who have undergone radiotherapy for painful bone metastases. EAS deserves further studies to be validated in exploring the consequences of any intervention producing a decrease in pain input during the course of disease.

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