



## Review Article

## Incidence of pain flare in radiation treatment of bone metastases: A literature review



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## ABSTRACT

**Purpose:** Pain flare is a temporary increase in pain and is a potential side effect of radiotherapy treatment. However, its incidence has been reported only in recent studies, and with great variability. A few studies have reported on the use of dexamethasone as a prophylactic agent in the prevention of pain flare. The objective of this study is to present a review of the available literature regarding the incidence of pain flare and use of dexamethasone as a preventative measure.

**Methods:** A literature search was conducted in PubMed using subject keywords including: "radiation therapy", "stereotactic radiation therapy", "bone metastases", "pain flare", and "dexamethasone". The search was limited to English only but not restricted to any time period. Additionally, a search was also conducted in the American Society for Therapeutic Radiology and Oncology (ASTRO) 2014 book of published abstracts. Inclusion criteria were primary studies published with full text and/or abstracts only. Letters to the editor were excluded.

**Results:** A total of 11 studies were selected, two of which were abstracts published by ASTRO in 2014. Seven articles investigated pain flare and/or dexamethasone use for conventional external beam radiation therapy (EBRT) while the remaining four investigated stereotactic body radiation therapy (SBRT). Pain flare incidence ranged from 2 to 44% for EBRT and 10 to 68% in SBRT. The use of dexamethasone also showed to be effective in both the prophylaxis and treatment of pain flare.

**Conclusions:** Pain flare has been established as an acute toxicity of both EBRT and SBRT, although its incidence is widely variable due to differences in data collection. The use of dexamethasone in the prophylaxis of pain flare is efficacious. Future studies are required in order to both optimize the reporting of pain and the dexamethasone regimens in the prevention of pain flare.

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## 1. Introduction

Bone metastases are exceedingly common among advanced cancer patients, especially in those with breast, prostate, and lung carcinomas [1,2]. They are a cause of great morbidity and result in significant pain in 50–75% of patients at some point throughout the course of their illness [2–4]. Bone metastases can also lead to hypercalcemia, skeletal complications including pathological fractures and spinal cord compression, and have a negative impact on quality of life (QOL) [1,5,6].

External beam radiation therapy (EBRT) is recommended for the relief of symptomatic bone metastases [1,5,6]. Studies have proven it to be both cost-effective and efficacious, with up to 80% of treated patients experiencing at least some pain relief [3,6].

Moreover, it has few associated toxicities, many of which are temporary and minor in nature [6].

Recent technological developments have led to an increased use of stereotactic body radiation therapy (SBRT) for the treatment of select tumors, most commonly to the liver, lung, or bone [7,8]. This technique is employed with a locally curative intent and delivers more radical doses of radiation with great accuracy [9]. For spinal metastases, SBRT allows for locally ablative doses of radiation to the target and limits the spinal cord or cauda to thresholds below the dose of myelopathy [6]. SBRT to the spine delays tumor progression and provides long-term pain control and maintenance or even improvement in QOL [7]. Long term complications of spine SBRT, unique from conventional EBRT, include vertebral compression fractures and, much less likely, radiation myelopathy. Acute adverse events are similar to conventional radiotherapy and are usually self-limiting [8].

Pain flare, defined as a "temporary worsening of bone pain in the treated metastatic site" [2], has been previously documented as a side effect of radiopharmaceutical and hormonal therapy [2,10,11]. Although it is a recognized side-effect of radiation treatment as well,

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only recent studies have attempted to accurately document its incidence in patients treated with EBRT or SBRT [2,4,7–13]. These studies report incidences reaching as high as 68% for SBRT and 44% for EBRT [8]. A qualitative study published by Hird et al. [14] discusses patient perspectives and the impact of pain flare on QOL. Overall, patients describe interference with daily activities and general functioning, as well as anxiety and worry regarding the success of the treatment. Typical pain flare management entails an increase in analgesic use, leaving the patient at risk of associated adverse events including dry mouth, drowsiness, and constipation [14]. Moreover, the majority of patients felt that their pain was not adequately relieved by increased analgesics. Rather, 85% of patients stated that the optimal management of pain flare requires prophylaxis [14].

Dexamethasone is an anti-inflammatory steroid medication that has been shown to be effective as a prophylactic agent against pain flare [4,8,12]. It is hypothesized that the dexamethasone reduces edema within the periosteum of the treated bone [15]. With a half life of 36–54 h, it may be administered to patients throughout the duration of treatment and for a few days post treatment in order to curb the debilitating effects of pain flare [12].

The objective of this report is to present the currently available literature documenting the incidence of pain flare in both conventional and stereotactic radiation therapy techniques. Furthermore, it will summarize the use of dexamethasone in early clinical trials as a prophylactic measure against the occurrence of pain flare.

## 2. Methods

A literature search was conducted in PubMed. It was limited to English articles only, but was not restricted to any time period. The American Society for Therapeutic Radiology and Oncology (ASTRO) 2014 book of published abstracts was also screened for potential relevant studies. Keywords and subject headings for searches included “radiation therapy”, “stereotactic radiation therapy”, “bone metastases”, “pain flare”, and “dexamethasone”. Inclusion criteria were primary studies published with full text and/or abstracts only. Letters to the editor and commentaries were excluded.

Abstracts and articles generated by the search were screened based on title first, then abstract or full text, independently by RM and LR. If there was a disagreement for inclusion or exclusion of an article, a discussion ensued until a consensus was reached.

## 3. Results

A total of eleven studies published between 2005 and 2014 were identified as relevant. This includes nine full text articles and two abstract publications extracted from the ASTRO 2014. Seven studies investigated EBRT with two additionally investigating prophylactic treatment of pain flare with dexamethasone and one investigating prophylaxis with a methylprednisolone infusion. Four studies investigated pain flare resulting from stereotactic radiation therapy, only one of which included dexamethasone as a prophylactic agent. A summary of the studies and their characteristics is presented in Table 1. The incidence of pain flare, duration of pain flare, and possible use of dexamethasone, if applicable, is reported in Table 2.

### 3.1. External beam radiation therapy

A total of seven studies have documented the incidence of pain flare in patients treated with EBRT to symptomatic bone metastases, three of which included an investigation of pain flare prophylaxis with a steroid medication [2,4,10–13,16]. All studies collected data such as pain score and analgesic intake prospectively using questionnaires at baseline, daily during, and daily after treatment completion for a set

duration of time. Specific data collection methods can be found in Table 1.

The first study to investigate the incidence of pain flare was published in 2005 [10]. Pain flare was defined in their study as either a 2-point increase in worst pain on a scale of 0–10 with no decrease in analgesic intake, or as a 25% increase in analgesic intake with no decrease in worst pain score. Between June 2000 and February 2001, 88 patients were accrued to the study. The incidence of pain flare was 14% on day one for patients who received 8 Gy in 1 fraction, and 15% on day one for patients who received 20 Gy in 5 fractions [10].

Following up with this study in 2007, the authors [12] published a study investigating the use of dexamethasone for the prophylaxis of pain flare. All 33 patients accrued to the study were prescribed two tablets of 4 mg dexamethasone by mouth one hour before treatment. Using the Brief Pain Inventory (BPI) to collect analgesic information and worst pain score, pain flare incidence in this population was reported to be 24% [12].

In contrast to the previous two studies, Loblaw et al. [11] collected pain scores using the Present Pain Intensity (PPI) questionnaire and developed two working definitions of pain flare: (1) a 2-point increase in the PPI with no decrease in analgesic score, or a 50% increase in analgesic score with no decrease in PPI on at least two consecutive days; and (2) a 2-point increase in PPI with no decrease in analgesic score or a 25% increase in analgesic score with no decrease in PPI on at least two consecutive days. The authors collected pain scores prospectively using the PPI at baseline, in a daily diary for the first week following treatment, and then at 14, 30, and 60 days post treatment. The incidence of pain flare was 34.1% and 40.9% using each definition, respectively [11].

Hird et al. [2] published a comprehensive study in 2009 with results on pain flare incidence from three Canadian Centres. A total of 111 patients were included in the study, of which 41% documented pain flare. Eighty percent of those who experienced pain flare also reported it to be within the first five days following treatment. A phase II trial was then published in 2009 by Hird et al. [4], in which 8 mg of dexamethasone was prescribed to all patients and taken at least one hour before daily radiotherapy and for three consecutive days following completion. Twenty-two percent of the 41 accrued patients reported pain flare with a median duration of one day.

A recent study published in abstract form only reported the incidence of pain flare in patients treated with EBRT to bone metastases [16]. This study collected worst pain scores and analgesic consumption prospectively before, daily during, and for ten days post-treatment. Of a total patient population of 94, 42 (44.7%) were documented to have pain flare. The median duration of pain flare was two days and the majority (88%) occurred between days one to five post-treatment [16].

In a double-blind randomized study, one hundred twenty patients with vertebral metastases during the two week short-course EBRT were randomized to methylprednisolone versus placebo resulting in pain flare incidence of 6.6% versus 20% respectively [13].

### 3.2. Stereotactic body radiation therapy

Four studies investigated the incidence of pain flare in patients treated with SBRT [7–9,17]. Three of the four studies defined pain flare as (1) at least a 2-point increase in worst pain score, (2) at least a 25% increase in opioid intake, or (3) the initiation of steroids [7,8,17]. The fourth study measured pain flare according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [7].

Chiang et al. [8] published the first study in March 2013 and focused specifically on SBRT for patients with spinal metastases. Data was collected prospectively using the BPI at baseline, during treatment, and ten days post follow-up. The authors found that 28 of 41

**Table 1**

Characteristics of the literature investigating pain flare incidence and use of dexamethasone.

Author (year)	Technique (EBRT/SBRT)	Study design and data collection (retrospective/prospective)	Population	Pain flare definition	Ref.
Chow (2005)	EBRT	Prospective, medications and pain score on a 0–10 score were collected at baseline, daily during treatment, and daily for 10 days post treatment	June 2000–Feb 2001 n=88	A 2-point increase in pain scale of 0–10 (0 meaning no pain, 10 meaning worst possible pain) with no decrease in analgesic intake or 25% increase in analgesic intake with no decrease in pain score. Pain score and analgesic intake must return back to normal to differentiate pain flare from pain progression	[10]
Chow (2007)	EBRT	Prospective, medications and pain score were recorded using the BPI at baseline, and daily for 10 days following treatment	n=33 Patients treated with 8 Gy/1 to bone metastases	A 2-point increase in pain scale of 0–10 (0 meaning no pain, 10 meaning worst possible pain) with no decrease in analgesic intake or 25% increase in analgesic intake with no decrease in pain score. Pain score and analgesic intake must return back to normal to differentiate pain flare from pain progression	[12]
Loblaw (2007)	EBRT	Prospective, medications were recorded and pain collected using the Present Pain Intensity (PPI) at baseline, in a daily diary for the first week following treatment, at 14 days, 1 month, and 3 months post treatment	Jan 29, 1997–Jan 20, 1999 n=44	Firstly as a 2-point increase in the PPI with no decrease in analgesic score or a 50% increase in analgesic score with no decrease in PPI on at least two consecutive days. Also defined as a 2-point increase in PPI with no decrease in analgesic score or a 25% increase in analgesic score with no decrease in PPI on at least two consecutive days	[11]
Hird (2009)	EBRT	Prospective; pain and medications were recorded with the BPI at baseline and then using a daily diary during treatment and 10 days after completion of treatment	Feb 2006–May 2008 n=111	A 2-point increase in pain scale of 0–10 (0 meaning no pain, 10 meaning worst possible pain) with no decrease in analgesic intake or 25% increase in analgesic intake with no decrease in pain score. Pain score and analgesic intake must return back to normal to differentiate pain flare from pain progression	[2]
Hird (2009)	EBRT	Prospective; pain, medications, and quality of life recorded through the BPI and EORTC QLQ-C30 at baseline, daily for 10 days, and at 6 weeks following treatment	Jan 2007–July 2008 n=41	A 2-point increase in pain scale of 0–10 (0 meaning no pain, 10 meaning worst possible pain) with no decrease in analgesic intake or 25% increase in analgesic intake with no decrease in pain score. Pain score and analgesic intake must return back to normal to differentiate pain flare from pain progression	[4]
Gomez-Iturriaga (2014)	EBRT	Prospective; worst pain scores and analgesic consumption were collected before, daily during, and 10 days post treatment	June 2010–Dec 2013 n=94	A 2-point increase in pain scale of 0–10 (0 meaning no pain, 10 meaning worst possible pain) with no decrease in analgesic intake or 25% increase in analgesic intake with no decrease in pain score	[16]
Yousef (2014)	EBRT	Prospective; BPI collected at baseline. Worst pain scores and analgesic information collected before, daily during, and at the end of follow-up	Nov 2012–May 2013 n=120, with vertebral metastases	A 2-point increase in worst pain score with no decrease in analgesic intake or a 25% increase in daily analgesic intake with no decrease in worst pain score	[13]
Chiang (2013)	SBRT	Prospective, data collected using BPI at baseline, during, and for 10 days following treatment	Feb 2010–April 2012 n=41	(1) A 2-point increase in worst pain score with no decrease in analgesic intake, (2) 25% increase in analgesic intake as compared with baseline, and no decrease in worst pain score, or (3) if corticosteroids were initiated during or after SBRT due to pain	[8]
Owen (2013)	SBRT	Retrospective, pain flare documented during follow-up clinic visits typically 1–3 months after treatment	Jan 1, 2008–Aug 1, 2012 n=74	Measured using the CTCAE v.4.03	[9]
Pan (2014)	SBRT	Retrospective, pain at metastatic sites measured using BPI (including current pain medications and concurrent medications). Follow-up with BPI occurred 1 and 2 weeks after treatment for single fraction courses, and 2 and 4 weeks after treatment for multiple fraction courses	2002–2011 n=195	First identified through clinical notes indicating an increase in pain at the site of treatment. By survey, defined as either (1) an ≥ 2-point increase in worst pain score, (2) an ≥ 25% increase in opioid intake, or (3) initiation of steroids	[7]
Khan (2014)	SBRT	Prospective; patients completed the BPI daily during treatment and for 10 days post treatment	Feb 2012–Feb 2014 n=47	A 2-point increase in worst pain score with no decrease in analgesic intake or 25% increase in analgesic intake as compared with baseline, and no decrease in worst pain score	[17]

(68.3%) accrued patients experienced pain flare and the most common occurrence was before day 3 following completion of treatment (71%) [8]. In contrast, Owen et al. [9] investigated SBRT for non-spine bone metastases. Data collection in this study was completed retrospectively; incidence of pain flare was determined from clinical notes based on follow-up visits typically one to three months after treatment

completion. A total of 74 patients were evaluable, and the reported incidence of pain flare was much lower at 10% [9].

A similar study design was used by Pan et al. [7] who completed a secondary analysis of phase I and II trials on spine SBRT. Pain scores were collected in a retrospective manner through completion of the BPI at baseline and one and two weeks after completion of single

**Table 2**

Characteristics of pain flare and use of dexamethasone.

Author (Year)	Incidence of pain flare (%)	Time to pain flare duration of pain flare	Intervention with dexamethasone	Ref.
<b>Chow (2005)</b>	14% on day 1 and 2 for patients who received a single treatment 15% on day 1 for patients who received 20 Gy/5 Overall range of pain flare from 2 to 16%	Most commonly experienced days 1 and 2 post-treatment (14% and 16%, respectively)	N/A	[10]
<b>Chow (2007)</b>	24% experienced pain flare during 10-day follow-up	Of the 24% who experienced pain flare, two of these patients experienced a one-day pain flare on day 3, three patients had 1-day pain flare on day 7, three had prolonged pain flare (one from day 2–4, one days 4–6, and one days 3–8) Median duration of three days	All patients were prescribed two tablets of 4 mg dexamethasone by mouth 1 h before radiation treatment	[12]
<b>Loblaw (2007)</b>	Using the first pain flare definition: 34.1% Using second pain flare definition: 40.9%		N/A	[11]
<b>Hird (2009)</b>	Overall incidence of 40%. For patients treated with 8 Gy/1, incidence was 39%, and for those treated with multiple fractions, the incidence was 41%.	Pain flare occurred within first 5 days following radiation in 80% of patients	N/A	[2]
<b>Hird (2009)</b>	22% experienced a total of 11 pain flares	Median duration of pain flare was 1 day, and these occurred on days 1, 2, and 4. Two separate 3 day pain flares occurred on days 6 and 8. Six of 11 (55%) pain flares occurred on day 5.	Dexamethasone was prescribed 8 mg orally at least 1 h before radiotherapy and 8 mg daily for 3 consecutive days after treatment	[4]
<b>Gomez-Iturriaga (2014)</b>	44.7%	Median duration of 2 days Majority of pain flares occurred days 1–5 (88%)	N/A	[16]
<b>Yousef (2014)</b>	6.6% in those who received a methylprednisolone infusion 20% in those who received placebo	Methylprednisolone Group: two patients with 1 day pain flare up on day 3, one patient with 1 day pain flare on day 7, one patient with 2 day pain flare on days 2–3 Placebo Group: five patients had 3 day pain flare days 4–6, other three had 6 day pain flare on days 4–9	A methylprednisolone infusion was administered to 60 patients for two hours before treatment. For the other 60 patients, placebo (saline solution) was infused.	[13]
<b>Chiang (2013)</b>	68.3%	Most commonly before day 3 following SBRT (71%)	n=13 started on rescue dexamethasone either during or within 10 days of completing treatment as a result of pain, after which pain scores decreased significantly over time	[8]
<b>Owen (2013)</b> <b>Pan (2014)</b>	10% 23%	N/A Overall median time to pain flare of 5 days; when determined by clinical evaluation median time to pain flare was 2.5 days	N/A Of 27 patients who were identified with pain flare by clinical evaluation, 16 (59%) were prescribed dexamethasone	[9] [7]
<b>Khan (2014)</b>	19% overall 25% in patients who received 4 mg (24) and 13% in patients who received 8 mg (23)	Occurred most frequently during and up to day 1 post treatment (66%)	Dexamethasone was prescribed to all patients, with 24 patients prescribed 4 mg and 23 patients prescribed 8 mg. All patients took dexamethasone 1 hr prior to daily treatment and for 4 days post treatment	[17]

fraction SBRT, or two and four weeks after completion of multiple fraction SBRT. Of 195 patients treated, approximately 23% experienced pain flare. The overall median time to pain flare was five days according to survey, however this decreased to 2.5 days when based solely on clinical evaluation [7].

The only study to investigate the use of prophylactic dexamethasone for pain flare for SBRT patients was published in an abstract by Khan et al. [17]. Dexamethasone was taken a day prior to treatment, daily during treatment, and for four days post treatment. Group one consisted of 24 patients prescribed 4 mg dexamethasone, of which 25% experienced pain flare. Group two consisted of 23 patients who were prescribed 8 mg of dexamethasone and the incidence of pain flare was considerably less, at only 13%. Pain flare occurred most often during treatment and up to day one following completion (66% of patients). Data was collected prospectively through the completion of the BPI daily during treatment and for 10 days following completion [17].

#### 4. Discussion

Bone pain as a result of bone metastases is a well documented occurrence in advanced cancer patients [2–4]. Palliative external beam radiation therapy, and more recently stereotactic body

radiation therapy, are effective and well-tolerated treatments for the relief of cancer related bone pain [1,5,6]. Pain flare, a temporary exacerbation of pain closely following completion of treatment, is a recognized acute toxicity of both treatment techniques [2]. We completed a comprehensive review of the currently available literature documenting the incidence of pain flare and the prophylactic use of dexamethasone to decrease the incidence.

The method of data collection is an inherently critical factor in study design and can greatly influence study results and their interpretation. It is particularly relevant to this current review when examining the widespread discrepancies in pain flare incidence, particularly among SBRT studies. Both Pan et al. [7] and Owen et al. [9] collected data retrospectively and reported incidence rates of 23% and 10%, respectively. These incidences are considerably less than the 68% reported by Chiang et al. [8] in 2013, in a study that employed prospective collection methods. Retrospective studies in general may be subject to recall bias, where patients do not accurately recall the events that they have experienced. Especially when the goal of treatment is to provide pain relief, these patients may be more focused on the improvement of their symptoms rather than the transient exacerbation of them. Noteworthy are that conventional EBRT studies obtained data prospectively and the collective incidence of pain flare was consistently around 40%.

Dexamethasone, with its anti-inflammatory properties, has been shown to be an effective medication in the treatment of pain flare and is hypothesized to prevent the phenomenon as well [12]. Despite a lack of literature investigating this hypothesis, currently published phase I and II trials have provided compelling preliminary evidence for its use as a prophylactic agent in both EBRT and SBRT treatment settings. Khan et al. [17] conducted the first and only study where patients receiving SBRT to the spine were prescribed either 4 mg or 8 mg dexamethasone once daily during treatment and four days post-treatment. Pain flare incidence was reported at 25% and 13% for each dose, respectively. This is significantly less than the previously reported 68% of patients at the same institution with similar patients who experienced pain flare without any prophylaxis [8]. Similar to the study conducted by Khan et al. [17], dexamethasone prophylaxis of varying regimens was used by Chow et al. [12] and Hird et al. [4] in patients treated with EBRT. Incidence of pain flare in these studies decreased from an average of 40% to 22–24% [12].

Despite the apparent benefit of prophylactic dexamethasone in decreasing the incidence of pain flare, there is a lack of consensus on dosage, frequency, and duration of intake. The majority of pain flare incidence occurs within days one to five following completion of radiation treatment [2,4,16]. With a half life of 36–54 h, theoretically dexamethasone prescribed for four days post-treatment should effectively prevent pain flare up to and including day five [4,12]. Results published by Khan et al. [17] confirm this hypothesis, as patients prescribed 8 mg of dexamethasone during and four days post treatment had pain flare incidence of only 13%. The incidence of pain flare in EBRT studies after prophylactic dexamethasone use remains higher at approximately 22–24%, however, these studies prescribed dexamethasone only on the day of treatment, or on the day of treatment with three additional subsequent days [4,12]. The greater incidence of pain flare in these studies as compared to the study by Khan et al. [17] may be related to the shorter duration of dexamethasone.

In determining the best possible dose of dexamethasone, it is equally important to consider optimal prophylaxis as well as adverse events and contraindications related to the medication itself. For instance, dexamethasone has a role in immune-suppression, which may lead to increased susceptibility for infection [18]. In already vulnerable populations such as those with advanced cancer, this risk must be weighed appropriately. Dexamethasone may also increase blood sugar levels putting those with diabetes at risk, or activate and further complicate ulcers and other digestive problems [18]. Other common side effects of dexamethasone include an increased appetite, trouble sleeping, and excess fluid retention or swelling in the face, hands or feet [18]. Especially in palliative cancer patients, where the goal of treatment often focuses on maintenance or improvement of QOL, the dosage and duration of dexamethasone must be optimally suited to maximize the prevention of pain flare while minimizing further side effects from the medication itself.

Although the use of dexamethasone appears to be protective against pain flare, some patients still endure the painful side effect. This occurs in approximately 13% of patients receiving spine SBRT, as reported by Khan et al. [17], and 22% of patients receiving EBRT, as reported by Hird et al. [4]. Why is it that these patients do not benefit from the anti-inflammatory properties of dexamethasone as the majority of patients seem to? The answer to this question may be found in the analysis of biomarkers or DNA of the patient. Determining what these markers are and developing methods of prophylaxis for these patients should be objectives of future studies in order to provide the best possible care to all patients.

Two studies are ongoing that promise to be paramount in the prescription of dexamethasone in the prophylaxis of pain flare. NCIC CTG is currently investigating the use of 8 mg dexamethasone daily on the day of treatment and four days post-treatment

versus placebo of the same duration (NCT01248585) [19]. The primary outcome of this study is the incidence of pain flare, with secondary outcomes including changes in pain scores, analgesic use, and QOL. The results of this study may be able to help identify those patients who will not benefit from prophylactic dexamethasone. Similarly, Westhoff et al. [15] are collaborating with twelve radiotherapy departments in the Netherlands to investigate placebo for four days versus 8 mg dexamethasone for one day with placebo for three days, versus 8 mg dexamethasone for four days (NCT01669499). Again, the primary outcome is the incidence of pain flare, with secondary outcomes including pain scores, QOL, and side effects. Similar studies should be undertaken in a stereotactic body radiation therapy setting, in order to confirm the findings by Khan et al. [17].

## 5. Conclusion

Bone metastases are very prevalent in advanced cancer patients and often lead to significantly debilitating pain. Radiation therapy is an effective treatment of painful bone metastases and is often well tolerated with little toxicity. However, acute pain flare has been previously recognized and is reported to have an incidence as high as 68% in SBRT and ~40% in patients treated EBRT. Dexamethasone appears to decrease the incidence of pain flare. Ongoing clinical trials will confirm the utility of dexamethasone and shed some light on the optimal duration, dose and frequency required to prevent pain flare.

## Conflict of Interest statement

The authors declare that there are no conflicts of interest.

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