Palliative Radiotherapy: Bone Metastases and Spinal Cord Compression

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BACKGROUND

Bone metastases are the most common cause of cancer-related pain (1). Among solid cancers, prostate, breast, thyroid, lung, and renal cell carcinoma account for 80 percent of all skeletal metastases (1-3). The prognosis for patients with bone metastases depends on the site of the primary disease: reported median survival is generally longest for patients with breast and prostate cancer, and shortest for patients with lung cancer (4).

Bone metastases can be described as complicated or uncomplicated, where uncomplicated generally refers to the absence of: impending or established pathological fracture, previous surgical fixation, impending or established spinal cord compression, impending or established cauda equina or nerve root compression (including cranial nerves), neuropathic pain, previous radiation, or associated soft tissue mass. Approximately one-third of bone metastatses are considered to be 'complicated' (5). Oligometastatic disease describes an intermediate state between disease that is localized to the primary site, and widespread metastases (6,7). The specific definition of oligometastases varies but in this review and as used by others, it means five or fewer metastatic lesions (7). Skeletal-related events typically encompass pathologic fracture, spinal cord compression, surgical intervention or use of palliative radiotherapy (RT) (8).

The treatment of an asymptomatic bone metastasis may be deferred unless the patient develops pain or is at risk for a skeletal-related event. . The treatment of bone metastases may involve several types of systemic interventions, including chemotherapy, hormonal therapy, bisphosphonates, or radioisotopes, in addition to local interventions such as external beam radiotherapy (EBRT), stereotactic body radiotherapy (SBRT) hemibody irradiation (HBI), radioisotopes, surgery, or percutaneous vertebral augmentation depending on the site and extent of disease, histology and biomarker profile of the metastasis (4).

Recognizing that patients with bone metastases may benefit from a multidisciplinary palliative/supportive care team(including physiotherapy therapy/ occupational therapy/ psychosocial/ speech-language pathology ect.), the intent of this guideline is to focus specifically on radiotherapy options. This guideline discusses palliative-intent radiotherapy treatment for complicated and uncomplicated bone metastases and the management of spinal cord compression. Whenever possible, participation in a clinical trial is strongly encouraged.

GUIDELINE QUESTIONS

- What roles do EBRT, stereotactic body radiotherapy (SBRT), HBI, and radioisotopes play in the management of uncomplicated and complicated bone metastases?
- When is repeat radiotherapy indicated and how should it be delivered?
- How should patients with spinal cord compression be managed?
- What is the role of steroids in the prophylaxis of radiation-induced pain flare after treatment of bone metastases?

DEVELOPMENT AND REVISION HISTORY

The original guideline was developed in 2008 by the clinical leaders of the Fast Track Palliative Radiotherapy Clinic for Bone Metastases in Calgary and the Palliative Radiation Oncology program in Edmonton, with input from provincial radiation oncologists. For the 2010 updates, evidence was selected

and reviewed by a working group comprised of radiation oncologists from Alberta Health Services – CancerControl Alberta and a Knowledge Management Specialist from the Guideline Resource Unit. Literature was reviewed in 2012, but no updates to the guideline were made. In 2016 the larger guideline was divided into several smaller guidelines and updated/new data incorporated after the completion of a systematic literature review. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

SEARCH STRATEGY

For the 2016 update, the National Library of Medicine's Pubmed database was systematically searched (January, 2012 to December, 2014) using 11 independent searches (Full details in Appendix A). In brief, articles were excluded if they: were not written or translated into English, were case studies involving less than 10 patients, or if the study involved pediatric patients. The references cited in articles identified through the formal searches were also scanned for additional sources. In total, 19 articles were identified and reviewed in detail for potential inclusion in the guideline based on a title/abstract screen. During the development of this guideline, studies published after 2014 were included as they became available.

TARGET POPULATION

Patients who are at least 18 years of age with bone metastases (complicated or uncomplicated), or impending or established spinal cord compression.

RECOMMENDATIONS

Summary of Recommendations:

External Beam Radiation

- EBRT improves pain and quality of life (QOL). Generally patients who experience pain relief also experience improvements in functional interference, physical and role function. EBRT provides at least some relief from pain in 60-85% of patients, with complete relief reported in 15-58%.
- Single fraction (8Gy) is recommended as standard therapy for uncomplicated bone metastases.
- For bone metastases associated with neuropathic pain, either 8Gy in one fraction or 20Gy in five fractions is recommended.
- A multi-fraction schedule is recommended in impending or established pathologic fracture who are not candidates for, or decline, surgical intervention, and for all other complicated bone metastases presentations in patients where treatment is clinically indicated. .
- Repeat EBRT may be considered at a minimum interval of four weeks if: no pain relief was achieved after the first course of radiation; if there was a partial response to first radiation but a better response is desired; or symptom progression occurs after partial or complete response to the first course of radiation therapy.

Hemibody irradiation

- Either a single or multi-fraction course of HBI may be considered for palliation of widespread bone metastases , with appropriate premedication. A dose of 6Gy for upper body and 8Gy for lower body is recommended. Sequential treatment of both the upper and lower body requires a four to six week gap for interval recovery of myelosuppression.

Radioisotopes

- The radioisotopes strontium-89 and samarium-153 should be considered if patients are not candidates for multiple local radiotherapy fields or HBI.

- Radium-223 may be an option for patients with castration resistant prostate cancer, however, radium-223 is not currently funded in Alberta.

Spinal Cord Compression

- Instability of the vertebral column and/or acute onset paresis should be treated immediately (within 24 to 48 hours) with surgical decompression and/or stabilization followed by post-operative radiotherapy.
- EBRT should be considered in patients with impending spinal cord compression, as well as instituted urgently in those with established spinal cord compression, who are not candidates for surgery.
- In patients with recurrent spinal cord compression in a previously irradiated region, repeat EBRT using conformal techniques can be performed depending on the interval from first treatment, though surgical decompression should be considered as a first option.

Steroids in Prevention of Pain Flare

- For those patients able to tolerate dexamethasone who will receive 8Gy/1 palliative EBRT, dexamethasone (8mg orally daily for five days starting one hour prior to treatment) is an effective prophylactic agent for the prevention of pain flare.

I. BONE METASTASES:

Recommendations for External Beam Radiation

1. Multiple studies have reported improved health-related QOL and functional interference after palliative EBRT for bone metastases (9-13). In general, patients who report decreased pain after palliative RT also experience significant improvements in degree of functional interference, physical and role function (9). As a result of decreases in associated symptoms such as insomnia and constipation, responders describe improved emotional functioning, general activity, normal work, and improvements in global QOL (9-12). Overall response to EBRT is approximately 60-85%, with 15-58% experiencing complete relief (14). If no improvement in bone metastases related pain occurs within the first 6 weeks of treatment, it is not likely to occur (13), and re-irradiation can be considered (see Recommendations for Repeat External Beam Radiotherapy below). For dose/fractionation recommendations, please see the specific sections on complicated and uncomplicated bone metastases, below.

Recommendations for Stereotactic Body Radiotherapy (SBRT):

2. SBRT is a highly conformal therapies have emerged as treatment options which permit the administration of ablative doses of radiation therapy to a tumour, typically in a single or a few fractions, while avoiding excessive doses to surrounding critical normal tissues. SBRT requires precise image-guidance and patient immobilization (15,16). SBRT is being used increasingly for *de novo, curative-intent* treatment (e.g. stage I lung cancer in patients not fit for surgery), retreatment of bone metastases near the spinal cord, and postoperative treatment to the surgical cavity following resection of brain metastases. Prospective cohort and retrospective series describe rates of local control, progression-free survival and palliation of 70-95% (17,18). SBRT requires specialized equipment, detailed treatment planning and rigorous treatment quality assurance, and thus should not be considered as first-line therapy in oncologic emergencies such as spinal cord compression. There are no completed RCTs on the optimal role of SBRT (19). Enrolling fit patients on clinical trials at centres with sufficient experience to provide high-

quality SBRT, should be encouraged (20). A number of phase II and III trials evaluating the role of SBRT for bone metastases or in other sites are currently open in Alberta.

3. HBI is an effective palliative treatment for symptoms associated with widespread symptomatic bony metastases (21-23), often described as painful lesions on both sides of the diaphragm.

4. Either a single or multifraction course of HBI may be considered for the palliation of pain (24). Single fraction HBI provides pain relief in 70-80% of patients, with some evidence to suggest a decreased need for opioids and subsequent local EBRT (21,25-29). HBI treats lytic, blastic and extraosseous lesions. HBI may be delivered either to the upper half (base of skull to iliac crest; 6Gy/1 fraction) or lower half of the body (iliac crest to ankles; 8Gy/1 fraction). ASTRO guidelines suggest HBI as an option for patients who would otherwise be candidates for radioisotope therapy (see below) but who reside in geographic areas where they are not readily available or when they are medically contraindicated (14).

5. HBI is associated with transitory but potentially severe hematopoietic and gastrointestinal tract toxicity (21). Patients should be premedicated with intravenous fluids, antiemetics and corticosteroids, and provided with analgesics in the event of pain flare (28,30,31). Sequential treatment of both the upper and lower body requires a four to six week gap for interval recovery of myelosuppression.

Recommendations for Radioisotopes:

Radioisotopes to treat bone metastases are radioactive elements administered intravenously that deliver radiation through selective absorption by metastatic bone sites. Radioisotopes can be administered on an outpatient basis and are used to treat multiple sites of blastic metastatic bone disease simultaneously (32,33).

6. Strontium-89 and samarium-153 are both effective in providing pain relief, and work equally well in various cancers without evidence of a dose response (32,34,35). Symptom response can take two to three weeks, with complete relief in 20-30%, partial response in 40-60%, and a mean duration of pain relief of up to six months (35,36). Pain flare occurs in approximately 10%. Myelosuppression is usually grade two or less and self-limited, with recovery in eight to twelve weeks (37). One meta-analysis reported overall toxicity of 15%. Strontium-89 may be particularly useful in hormone refractory metastatic prostate cancer when painful bone metastases are poorly controlled by opioid analgesics and patients are not candidates for multiple local EBRT fields or HBI (37). Early studies of Rhenium-188 also suggest efficacy (38,39). ASTRO consensus guidelines recommend use of radioisotopes when patients have several sites of painful osteoblastic metastases in an anatomic distribution greater than that which could be conveniently treated with local field EBRT. There is also some evidence that strontium-89 is cost-effective compared to local EBRT alone (40,41). Patient eligibility criteria are strict however (i.e., minimum performance status and laboratory values, painful sites of disease on both sides of the diaphragm), and radioisotopes should not be used in the presence of pathologic fracture, spinal cord compression, hypercalcemia, or nerve root compression (42). They may not be available in all centres.

7. The evidence for alternating a radioisotope after a lack of response to a different one is poorly defined. The role of strontium as an adjunct to palliative EBRT remains uncertain (43).

8. Radioisotopes may preclude further systemic chemotherapy or eligibility for clinical trials of systemic therapy. Further research is needed to examine the use of radioisotopes in combination with systemic

therapies, although a recent phase I trial of Rhenium-188 alternating with docetaxel reported this combination to be generally well-tolerated (39,41).

9. Although not funded in Alberta, Radium-223 improves overall survival versus placebo ($p<0.001$) in men with castrate-resistant prostate cancer with bone metastases who had completed, were not eligible for, or declined docetaxel (44). Radium-223 also increased the time to first symptomatic skeletal event ($p<0.001$), and improved overall QOL ($p=0.006$) when compared to placebo (44). A dose escalation study of Radium-223 reported decreased pain in up to 71% of patients by eight weeks post-treatment with all dose levels well-tolerated (45).

Recommendations for Radiofrequency Ablation:

10. Radiofrequency ablation (RFA) is a form of electrosurgery which uses high-frequency radiowaves (>10 kHz) emitted through an electrode tip implanted in human tissue to generate heat. This process creates a precisely targeted area of necrosis via the induction of coagulation. RFA has been used in a number of tumour sites including bone metastases (46), resulting in safe and predictable outcomes (N=12; significant reduction in mean pain before vs. after RFA $p=0.002$). RFA is limited by the proximity of the metastases to neurological structures, and should not be used in large lesions of weight-bearing bones. Preliminary data from two small studies (total N=51) on RFA followed by either cementoplasty or short course EBRT suggests that multimodality treatment is safe, practical and potentially effective in decreasing pain (47,48).

Recommended Dose/Fractionation for Uncomplicated bone metastases:

11. 8Gy in one fraction is recommended for the treatment of uncomplicated bone metastases (12,14,49-51). Numerous randomized controlled trials (RCT) published over the past three decades have consistently demonstrated the equivalence of single and multiple fraction schedules for the palliation of pain (4). 8Gy has been compared to other single fraction doses, demonstrating in general, numerically superior pain response rates compared to doses less than 8Gy, and has an established safety profile (52). Meta-analyses of these trials have repeatedly shown no significant differences between single fraction and multi-fraction RT regimens with regards to rates of pathological fractures, spinal cord compression, QOL, acute toxicity, time to first improvement in pain, time to complete pain relief, time to pain progression, or opioid use (4,53-55). From a health systems perspective, single fraction EBRT is convenient for patients and cost-effective in comparison to multi-fraction RT or SBRT (56). Patients receiving single fraction RT as compared to multi-fraction RT are somewhat more likely to receive a repeat course of RT to the same site(4,53-55). There is insufficient evidence to recommend a specific dose fractionation schedule for oligometastatic disease (54) although effectiveness of single fraction EBRT in patients with a life expectancy of $\geq$12 months has been established.

Recommendations for the use of prophylactic Dexamethasone to prevent pain flare following palliative RT

12. Dexamethasone is an effective prophylactic agent for the prevention of pain flare after palliative EBRT for bone metastases (57,58)(59). In a randomized trial (58) Dexamethasone was administered as 8mg orally one hour prior to single fraction radiation and daily for four consecutive days subsequently, without a taper. In patients with complete follow-up data, 18% reported pain flare on the dexamethasone arm compared to 29% on the placebo arm ($p=0.01$). Patients on the dexamethasone arm who did

experience pain flare had less severe pain for a shorter duration of time. At day 10 after radiation, patients on the dexamethasone arm reported less functional interference and nausea, and improved appetite. There was no significant difference in reported side effects at day 10. The number needed to treat to prevent pain flare is nine. Dexamethasone should therefore be considered as standard premedication in all patients with solid tumours receiving single fraction EBRT for painful bone metastases provided they do not have contraindications to the use of steroids. For those patients still experiencing pain flair, principals of pain management should be followed.

13. Patients should be provided with analgesics in case of pain flare. Dexamethasone may be an effective prophylactic agent for the prevention of pain flare after palliative radiotherapy for bone metastases although to date it use has only been studied in patients with uncomplicated bone metastases (57,58).

Recommended Dose/Fractionation for Complicated bone metastases:

14. For bone metastases causing neuropathic pain, either 8Gy in a single fraction or 20Gy/5 fractions are recommended (60). Most guidelines recommend fractionated EBRT in a patient with an impending or established fracture who is not a candidate for surgical intervention (2,54), and for post-operative treatment. There is insufficient evidence to recommend a specific dose fractionation schedule for treatment of soft tissue masses associated with bony disease or other complicated bone metastases (54), although generally multiple fractions are administered presuming sufficient PS (See spinal cord compression section below).

15. **Postoperative radiotherapy**, usually delivered at a dose of 20Gy/5 or 30Gy/10 fractions, suppresses tumour growth and prevents destabilization of a prosthesis by maintaining the structural integrity of the bone in which it is fixed (52, 52). Post-operative EBRT also decreases pain, increases the frequency of normal use of the extremity, decreases the likelihood of revision procedures/implant failure, minimizes the risk of disease progression, and reduces the risk of re-fracture (53). Generally, it is initiated 2-4 weeks post-surgery. Wound complications are rare.

Recommendations for Repeat External Beam Radiation therapy:

16. Repeat EBRT can be offered in the following clinical situations:

(a) No pain relief after a first course of radiation therapy,
(b) Partial response after a first course of radiation therapy, but a better response is desired, or
(c) Symptom (or in some cases radiologic) progression after either partial or complete response to a first course of radiation therapy (61).

Repeat EBRT may be considered especially if other modalities, such as surgery or systemic therapy, are contraindicated or anticipated to be ineffective. Many authors suggest that four to six weeks is the minimum time interval to maximum response after EBRT. Therefore, retreatment should be delayed until this time, which also allows response to the first course to be adequately assessed and pain flare to have resolved (62). The Canadian Cancer Trials Group (CCTG; formerly NCIC CTG) SC20 trial randomized 850 patients (557 evaluable) receiving repeat RT to either 8Gy/1 or 20Gy/5 (20Gy/8 for the spine or whole pelvis) (24). Response rates at 2 months after 8Gy (28%) was non-inferior to 20Gy (32%) by intent-to-treat analysis, but findings were not robust to per-protocol sensitivity analysis. Day 14 adverse events differing by dose were: lack of appetite (P=0.01), vomiting (P= 0.001), diarrhea (P=0.02) and skin erythema (P=0.002); all worse with 20Gy/5 fractions. There were 30 vs 20 pathological fractures and 7 vs 2 spinal cord compressions with 8Gy and 20Gy, respectively (NS). When choosing between these

options, trade-offs exist between pain response and acute toxicity (63). In the CCTG SC20 trial From baseline, walking ability was significantly improved. and cognitive function and fatigue showed a trend towards significance. Patients who responded to treatment showed improved activity, mood, normal work, relations with other people, sleep and enjoyment of life. Responding patients also demonstrated improvements in physical, emotional and social functioning, global QOL, fatigue, pain and appetite (64). Meta-analyses of repeat EBRT have reported similar pain response outcomes. Wong et al. reported a 20% complete, and 50% partial, response rate, whereas Huisman et al, reported a 58% overall response rate (61,65,66) . There was no grade 3 or 4 toxicity, approximately 15% grade 1-2 acute toxicity, and a 2.2% rate of subsequent spinal cord compression (61). As there seems to be no difference between single and multiple fraction schedules in terms of response, single fraction should be strongly considered at the time of retreatment.

Recommendations for Surgery, Percutaneous Vertebral Augmentation and Postoperative EBRT:

17. An impending fracture is defined as a bony metastasis that, if not addressed, has a significant likelihood of fracture under normal physiological stresses. Depending on individual and disease factors, patients with an impending or established fracture may benefit from surgery, EBRT or both (13,67). Surgical intervention requires adequate patient fitness and life expectancy, and recovery from surgery may delay other treatment modalities. Surgery would usually be followed by postoperative EBRT or SBRT, provided that the site has not been recently radiated.

18. Percutaneous vertebral augmentations are minimally invasive outpatient surgical techniques that are alternatives to open surgery for restoring stability to a subset of vertebral body lytic metastases, with resultant improvement in pain and mobility (68). These are both potential treatment options for patients who are not suitable for invasive surgery due to medical comorbidities, or multilevel disease, but cannot be used in the setting of an associated soft tissue mass causing spinal cord compression (69). The benefits of the combination of percutaneous vertebral augmentation with EBRT remain undefined (4). There is no evidence that the addition of either percutaneous vertebral augmentation improves symptoms or has other benefits on clinically significant endpoints compared to the use of EBRT alone (14).

Recommendations for Systemic Therapy:

19. **Pharmacologic therapy**. Pharmacologic therapy such as opioid analgesics has minimal contraindications, address multiple sites of pain, and can be tailored to the mechanism of pain. Side effects must be proactively addressed and doses monitored and titrated. Patients should be counselled proactively on the potential impact of both pain flare and pain response on analgesic intake.

20. **Systemic therapy**. Although radiation oncology is typically the treatment of choice, medical oncology can play an important role in the management of bone metastases and should be incorporated as part of the interdisciplinary team(51). Hormonal and chemotherapy treat systemic disease as well as bone metastases, and may prolong survival as well as improve QOL. The role for systemic anti-cancer therapy for the management of bone metastases should be assessed on a case by case basis.

II. SPINAL CORD COMPRESSION (including cauda equina syndrome)

Malignant epidural spinal cord compression (SCC) affect 2.5% overall of patients who died from cancer(70,71). Malignant epidural SCC is a medical emergency, and if left untreated, can lead to progressive pain, paralysis, sensory loss, and incontinence (72,73). The early diagnosis and treatment of patients with SCC is essential to optimize symptom control, preserve neurologic function and maximize QOL.

In adult patients, prostate, breast, and lung cancer each account for approximately 15 to 20 percent of cases of SCC; other less common associated cancers include non-Hodgkin lymphoma, myeloma, renal cell carcinoma, colorectal cancer, unknown primary site, and sarcoma (72,74,75).

SCC most often occurs in the setting of widespread metastatic cancer; several large retrospective reviews have reported a median survival of three to six months overall (76,77). Factors associated with a better prognosis include: time to development of motor deficits (78), ambulatory ability before and after therapy, radiosensitive histology, no visceral or brain metastases, and a single site of compression (72,79-81).

Target Population: Adult patients with impending or established malignant epidural SCC or cauda equina compression.

Recommendations for Impending Spinal Cord/ Cauda Equina Compression:

21. Retrospective data suggests that EBRT may preserve neurologic function in patients with radiological impending SCC (i.e., no neurologic deficits and back pain as the only symptom) (82,83). There is insufficient evidence at present to guide practice; however, consultation with both a radiation oncologist and spinal surgeon should be strongly considered before initiation of any therapeutic modality.

Recommendations for Established Spinal Cord/ Cauda Equina Compression:

22. Instability of the vertebral column due to fracture, subluxation or dislocation, and/or acute onset of paresis/paraplegia should be addressed immediately with urgent spine surgery consultation followed by post-operative EBRT, or EBRT alone when surgical intervention is not indicated or is declined by the patient (50). In addition, it is strongly recommended that a spinal surgery service be consulted for a surgical opinion in the following circumstances: tissue diagnosis required; solitary level of compression; neurologic deterioration during or after maximal dose RT; radioresistant tumour; or rapid evolution of symptoms or acute onset paraplegia (84-87). A 2005 randomized trial reported that decompressive surgery followed by postoperative radiotherapy (30Gy/10 fractions) was superior to RT alone for select patients with established malignant epidural SCC (50,86). In that trial, patients treated with surgery and radiotherapy had significantly better post-treatment ambulation rates, retention of ambulation and continence, maintenance of functional and motor scores, and lower median daily doses of steroids and analgesics, when compared to patients who received radiotherapy only. Survival and 30-day morbidity were also better, with no difference in 30-day mortality or length of hospital stay. That study was limited to patients with specific tumour histologies (lung, breast, prostate, other genitourinary, gastrointestinal, melanoma, and head and neck), displacement or compression of the spinal cord as seen on MRI, a single level of cord compression, and total paraplegia for less than 48 hours, and therefore the results are not applicable to all patients with malignant SCC (86). Although a combined modality approach results in better outcomes, treatment costs are increased (88). The age of the patient is also an important variable

to consider when selecting patients with SCC for surgical or non-surgical interventions. Preservation of ambulatory ability was significantly prolonged in patients younger than 65 years undergoing surgery plus radiotherapy compared to EBRT alone (p<0.002) (89). As surgical complication rates are dramatically higher in cases where surgery occurs after completion of EBRT(90) consultation with a spinal surgeon should be sought prior to commencement of radiation therapy in all cases where surgical intervention is deemed a reasonable possibility.

23. In patients who are not candidates for surgery, radiotherapy alone is the recommended treatment, although the optimal dose and fractionation schedule is not known (20,74). Treatment may provide pain relief rates of 55-60%, maintain ambulatory ability (defined as the ability to take at least two steps with each foot unassisted) in about 70%, and maintain neurological function in select patents. These patients generally have a median survival of 4.0 months (86). Two randomized trials in patients with poor PS have been published, neither of which involved dose-fractionation schedules which would be considered standard in Canada. In the first trial, a short-course regimen of 16Gy/2 fractions over one week was compared with a split-course regimen of 15Gy/3 fractions followed by a break and then 15Gy/5 fractions (84). No significant differences between the two groups were reported for relief of back pain, ambulation, bladder function, survival, toxicity or duration of motor improvement, although there was a suggestion of increased radiologic in-field recurrence in the short-course group. Based on these results, the authors suggested the use of a short-course of radiotherapy as the regimen of choice for patients with malignant SCC and a short life expectancy (84). In the second trial, 303 patients with malignant SCC and short life expectancy were randomly assigned to a short-course of either 8Gy/2 fractions over one week or 8Gy in a single fraction (85). After radiotherapy, 66% were able to walk, 86% had good bladder function, and 53% had pain relief with a median survival of four months and response which lasted until death in the majority of cases. There were no significant differences in response between the two groups. Results from the ICORG 05-03 trial published in abstract form support 10Gy single fraction EBRT as being equivalent to 20Gy in 5 fractions in patients who are ineligible for surgery. That phase III, non-inferiority trial, evaluated data from 76 patients of whom 10% experienced improvements in mobility and 58-68% experienced stabilization. There were no significant differences in bladder control, neurological deterioration-free survival or overall survival between the two arms, and grade 3/4 acute and chronic toxicity was similar between arms (91).

24. Some studies indicate that radiotherapy courses of five fractions or less are associated with significantly more in-field recurrences, data suggests that dose escalation past 30Gy is not clinically useful (74,78,87,92,93) and single fraction RT may be as effective as 5 fractions for many patients (91). Long-course radiotherapy with doses of 30 Gy in 10 fractions or more do not offer benefit compared with shorter regimens in terms of immediate neurological outcome or survival, but may result in fewer in-field recurrences, which could be an advantage in patients expected to live longer. Shorter courses are more cost-effective, less time-consuming and should be used for patients with extensive metastatic disease, a life expectancy of less than 3 months and for patients with poor PS (74,79).

25. In the setting of certain chemosensitive tumours, such as lymphoma or myeloma, systemic therapy should be considered the primary treatment modality, especially if disease is also present outside of the spine.

Recommendations for Recurrent or Progressive Spinal Cord Compression

26. Recurrence of malignant SCC in a previously irradiated region may be treated with repeat EBRT although surgical decompression should be considered in the setting of maximal previous RT. If

administering repeat RT, conformal techniques should be utilized to reduce the cumulative spinal cord dose (79).

Other Considerations not Covered in Detail
Consider avoiding radiotherapy near end of life when radiotherapy in unlikely to provide benefit for the patient and may cause acute toxicity which may negatively impact quality of life in the interim (e.g. when Palliative Performance Status <40%, or estimated prognosis is <1 month). For a more detailed review on when palliative radiotherapy should be avoided see (94).

GLOSSARY OF ABBREVIATIONS

Acronym	Description
HBI	Hemibody Irradiation
OS	Overall Survival
PS	Performance Status
QoL	Quality of Life
RT	Radio Therapy
SBRT	Sterotactic Body Radiotherapy

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

This guideline will be reviewed annually for required updates; however, if critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the working group in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the working group are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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APPENDIX A: FULL SEARCH STRATEGY

For the 2015 update, the National Library of Medicine's Pubmed database was searched (January, 2012 to December, 2014) using the following search terms (12 independent searches): (1) palliative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND ("neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "metastases"[All Fields]) AND external[All Fields] AND beam[All Fields] AND ("radiation"[MeSH Terms] OR "radiation"[All Fields] OR "electromagnetic radiation"[MeSH Terms] OR ("electromagnetic"[All Fields] AND "radiation"[All Fields]) OR "electromagnetic radiation"[All Fields]) (2) palliative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND uncomplicated[All Fields] AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND ("neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "metastases"[All Fields]) (3) palliative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND complicated[All Fields] AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND ("neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "metastases"[All Fields]) (4) (palliative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND ("radiosurgery"[MeSH Terms] OR "radiosurgery"[All Fields] OR "sbrt"[All Fields])) OR (sterotactic[All Fields] AND ("human body"[MeSH Terms] OR ("human"[All Fields] AND "body"[All Fields]) OR "human body"[All Fields] OR "body"[All Fields])) (5) reirradiation[All Fields] OR (re-irradiation[All Fields] AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND ("neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "metastases"[All Fields])) (6) (palliative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND hemibody[All Fields]) OR (half-body[All Fields] AND ("radiotherapy"[MeSH Terms] OR "radiotherapy"[All Fields] OR "irradiation"[All Fields])) (7) palliative[All Fields] AND ("radiation"[MeSH Terms] OR "radiation"[All Fields] OR "electromagnetic radiation"[MeSH Terms] OR ("electromagnetic"[All Fields] AND "radiation"[All Fields]) OR "electromagnetic radiation"[All Fields]) AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND ("radioisotopes"[MeSH Terms] OR "radioisotopes"[All Fields]) (8) (palliative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND ("neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "metastasis"[All Fields]) AND ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields]) AND impending[All Fields] AND ("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields])) OR ("postoperative period"[MeSH Terms] OR ("postoperative"[All Fields] AND "period"[All Fields]) OR "postoperative period"[All Fields] OR "postoperative"[All Fields]) OR

percutaneous[All Fields] OR ("vertebroplasty"[MeSH Terms] OR "vertebroplasty"[All Fields]) OR ("kyphoplasty"[MeSH Terms] OR "kyphoplasty"[All Fields]) (9) palliative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND radiofrequency[All Fields] AND ablation[All Fields] (10) palliative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND opiod[All Fields] (11) palliative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND ("diphosphonates"[MeSH Terms] OR "diphosphonates"[All Fields] OR "bisphosphonates"[All Fields]) (12) palliative[All Fields] AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND ("spinal cord compression"[MeSH Terms] OR ("spinal"[All Fields] AND "cord"[All Fields] AND "compression"[All Fields]) OR "spinal cord compression"[All Fields]). Articles were excluded if they: were not written or translated into English, were case studies involving less than 10 patients, or involved pediatric patients. The references cited in articles identified through the formal searches were also scanned for additional sources. In total, 19 articles were identified and reviewed in detail based on a title/abstract screen.