Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Janjan N, Lutz ST, Bedwinek JM, et al. Therapeutic guidelines for the treatment of bone metastasis: a report from the American College of Radiology Appropriateness Criteria Expert Panel on Radiation Oncology. *J Palliat Med.* 2009;12(5):417-426.	Review/Other-Tx	N/A	To create representative clinical case scenarios and then rank the appropriate use of treatment modalities as well as the most reasonable RT dose schema and treatment planning methods, presenting both the resulting Appropriateness Criteria and the rationale for making these decisions.	The treatment recommendations are placed within the larger framework of the role of radiation in palliative care by discussing the efficiency of palliative RT schedules, cost effectiveness issues, and the need for additional research regarding the proper multidisciplinary care of patients with symptomatic bone metastasis.	4
2. Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys.* 2011;79(4):965-976.	Review/Other-Tx	4,287 candidate original research articles	To present guidance for patients and physicians regarding the use of RT in the treatment of bone metastases according to current published evidence and complemented by expert opinion.	EBRT continues to be the mainstay for the treatment of pain and/or prevention of the morbidity caused by bone metastases. Various fractionation schedules can provide significant palliation of symptoms and/or prevent the morbidity of bone metastases. The evidence for the safety and efficacy of repeat treatment to previously irradiated areas of peripheral bone metastases for pain was derived from both prospective studies and retrospective data, and it can be safe and effective. The Task Force recommended that the use of SBRT be limited to highly selected patients and preferably within a prospective trial. RT is a successful and time efficient method by which to palliate pain and/or prevent the morbidity of bone metastases. This Guideline reviews the available data to define its proper use and provide consensus views concerning contemporary controversies or unanswered questions that warrant prospective trial evaluation.	4

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
3. Wu JS, Wong RK, Lloyd NS, Johnston M, Bezjak A, Whelan T. Radiotherapy fractionation for the palliation of uncomplicated painful bone metastases - an evidence-based practice guideline. *BMC Cancer.* 2004;4:71.	Review/Other-Tx	N/A	Guideline to provide recommendations to clinicians in Ontario on the preferred standard RT fractionation schedule for the treatment of painful bone metastases.	For adult patients with single or multiple radiographically confirmed bone metastases of any histology corresponding to painful areas in previously non-irradiated areas without pathologic fractures or spinal cord/cauda equine compression, it is concluded that: Where the treatment objective is pain relief, a single 8 Gy treatment, prescribed to the appropriate target volume, is recommended as the standard dose-fractionation schedule for the treatment of symptomatic and uncomplicated bone metastases. Several factors frequently considered in clinical practice when applying this evidence such as the effect of primary histology, anatomical site of treatment, risk of pathological fracture, soft tissue disease and cord compression, use of antiemetics, and the role of retreatment are discussed as qualifying statements. Qualifying statements addressing factors that should be considered when applying this recommendation in clinical practice facilitate its clinical application. The rigorous development and approval process result in a final document that is strongly endorsed by practitioners as a practice guideline.	4
4. Lo SS, Lutz ST, Chang EL, et al. ACR Appropriateness Criteria (R) spinal bone metastases. *J Palliat Med.* 2013;16(1):9-19.	Review/Other-Tx	N/A	Appropriateness Criteria on spinal bone metastases.	No results stated in abstract.	4
5. Lutz ST, Lo SS, Chang EL, et al. ACR Appropriateness Criteria(R) non-spine bone metastases. *J Palliat Med.* 2012;15(5):521-526.	Review/Other-Tx	N/A	Appropriateness Criteria on non-spine bone metastases.	No results stated in abstract.	4

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
6. Cancer Care Ontario Guideline on Radiopharmaceuticals for the Palliation of Painful Bone Metastases. http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34803. Accessed October 28, 2013.	Review/Other-Tx	N/A	Practice guidelines to describe the role of radiopharmaceuticals in the palliation of metastatic bone pain.	Randomized phase III trials have been reported for the use of radioactive strontium, samarium and rhenium, while radioactive tin and phosphorus have only been investigated in phase I/II trials at this time. Sr-89 has been investigated mainly in men with metastatic hormone-refractory prostate cancer, while the other radiopharmaceuticals have been investigated in a wider variation of cancer histologies. Metastatic breast cancer (approximately 5%–10% of patients reported), metastatic hormone-refractory prostate cancer (80%–90% of patients reported) or metastatic lung cancer (5%–10% of patients reported) represent the most common histologies. Information on histologic subtype was not available for a significant proportion of patients treated on trials (30%–40% of patients reported). Ongoing studies are required to evaluate newer radiopharmaceuticals (ie, radioactive tin and rhenium), compare existing radiopharmaceuticals (ie, strontium-89 vs samarium-153), determine the optimal dose and timing of radiopharmaceuticals, determine the efficacy of re-treatment with radiopharmaceuticals and compare radiopharmaceuticals with other agents such as EBRT and chemotherapy.	4

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
7. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369(3):213-223.	Experimental-Tx	921 patients	To assess the efficacy and safety of radium-223 as compared with placebo, in addition to the best standard of care, in men with castration-resistant prostate cancer and bone metastases.	At the interim analysis, which involved 809 patients, radium-223, as compared with placebo, significantly improved overall survival (median, 14.0 months vs 11.2 months; HR, 0.70; 95% CI, 0.55 to 0.88; two-sided P=0.002). The updated analysis involving 921 patients confirmed the radium-223 survival benefit (median, 14.9 months vs 11.3 months; HR, 0.70; 95% CI, 0.58 to 0.83; P<0.001). Assessments of all main secondary efficacy end points also showed a benefit of radium-233 as compared with placebo. Radium-223 was associated with low myelosuppression rates and fewer adverse events.	1
8. Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. *Clin Orthop Relat Res.* 1989(249):256-264.	Review/Other-Tx	78 lesions	Retrospective analysis to quantify the risk of sustaining a pathologic fracture through a metastatic lesion in a long bone.	The outcome identified 51 lesions that did not fracture during the subsequent 6 months and 27 lesions that fractured within 6 months. A mean score of 7 was found in the nonfracture group, whereas the fracture group had a mean score of 10. As the score increased above 7, so did the percentage risk of fracture. It is suggested that all metastatic lesions in long bones be evaluated prior to irradiation. Lesions with scores of 7 or lower can be safely irradiated without risk of fracture, while lesions with scores of 8 or higher require prophylactic internal fixation prior to irradiation.	4

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
9. van der Linden YM, Kroon HM, Dijkstra SP, et al. Simple radiographic parameter predicts fracturing in metastatic femoral bone lesions: results from a randomised trial. *Radiother Oncol.* 2003;69(1):21-31.	Experimental-Tx	1,157 patients	Randomized trial to identify lesional risk factors for fracturing and to evaluate the influence of the treatment schedule.	Ten fractures occurred after median 7 weeks in 44 single fraction patients (23%) and 4 after median 20 weeks in 58 multiple fraction patients (7%) (univariate analysis, P=0.02). In 110 femoral metastases, an axial cortical involvement >30 mm significantly predicted fracturing (multivariate analysis, P=0.02). 12/14 fractured lesions and 40/96 non-fractured metastases had an axial cortical involvement >30 mm (negative predictive value, 97%). When correcting for the axial cortical involvement, the treatment schedule was not predictive anymore (multivariate analysis, P=0.07). Fracturing of the femur mostly depended on the amount of axial cortical involvement of the metastasis. It is recommended to treat femoral metastases with an axial cortical involvement ≤30 mm with an single fraction of 8 Gy for relief of pain. If the axial cortical involvement is >30 mm, prophylactic surgery should be performed to minimize the risk of pathological fracturing or, if the patient's condition is limited, irradiation to a higher total dose.	1

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
10. Lo SS, Teh BS, Mayr NA, et al. Stereotactic body radiation therapy for oligometastases. *Discov Med.* 2010;10(52):247-254.	Review/Other-Tx	N/A	To review the literature to evaluate the presence of an oligometastatic state, and local aggressive therapy of the oligometastases may improve outcomes including survival.	SBRT represents one of the options for local aggressive therapy for patients with oligometastases in various body sites, most commonly in the lung and liver. A good amount of data from various studies, both retrospective and prospective, showed promising results. Most studies showed good local tumor control. In a limited subset of patients, relatively long survival could be achieved. One note of caution is that the follow-up times of most studies were relatively short and therefore, long-term outcomes are not yet available. Longer follow-up is necessary to better define the role of SBRT in the management of oligometastases. Currently, they are multiple ongoing clinical trials on the use of SBRT for oligometastases in various body sites and the results of those trials are eagerly awaited. Given the high propensity for distant progression, the combination of novel systemic therapy and SBRT is to be explored.	4
11. Chow E, Hoskin P, Mitera G, et al. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Int J Radiat Oncol Biol Phys.* 2012;82(5):1730-1737.	Review/Other-Tx	49 experts surveyed	To update the international consensus on palliative RT endpoints for future clinical trials in bone metastases by surveying international experts regarding previous uncertainties within the 2002 consensus, changes that may be necessary based on practice pattern changes and research findings since that time.	Consensus was established in areas involving response definitions, eligibility criteria for future trials, reirradiation, changes in systemic therapy, radiation techniques, parameters at follow-up, and timing of assessments. An outline for trials in bone metastases was updated based on survey and consensus. Investigators leading trials in bone metastases are encouraged to adopt the revised guideline to promote consistent reporting. Areas for future research were identified. It is intended for the consensus to be re-examined in the future on a regular basis.	4

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
12. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol.* 2007;25(11):1423-1436.	Review/Other-Tx	16 randomized trials	To update previous meta-analyses with a systematic review of randomized palliative RT trials comparing single fractions vs multiple fractions.	For intention-to-treat patients, the overall response rates for pain were similar for single fractions at 1,468 (58%) of 2,513 patients and multiple fractions RT at 1,466 (59%) of 2,487 patients. The CR rates for pain were 23% (545/2,375 patients) for single fractions and 24% (558/2,351 patients) for multiple fractions RT. Trends showing an increased risk for single fractions RT arm patients in terms of pathological fractures and spinal cord compressions were observed, but neither were statistically significant (P=.75 and P=.13, respectively). The likelihood of re-treatment was 2.5-fold higher (95% CI, 1.76 to 3.56) in single fractions RT arm patients (P<.00001). Repeated analysis of these end points, excluding dropout patients, did not alter the conclusions. Generally, no significant differences with respect to acute toxicities were observed between the arms. No significant differences in the arms were observed for overall and CR rates in both intention-to-treat and assessable patients. However, a significantly higher re-treatment rate with single fractions s was evident.	4
13. Fairchild A, Barnes E, Ghosh S, et al. International patterns of practice in palliative radiotherapy for painful bone metastases: evidence-based practice? *Int J Radiat Oncol Biol Phys.* 2009;75(5):1501-1510.	Review/Other-Tx	962 respondents 101 dose schedules described	To determine the current patterns of practice internationally and to investigate the factors influencing this practice.	The median dose overall was 30 Gy/10 fractions. Single fractions schedules were used the least often by ASTRO members practicing in the United States and most often by CARO members. Case, membership affiliation, country of training, location of practice, and practice type were independently predictive of the use of single fractions. The principal factors considered when prescribing were prognosis, risk of spinal cord compression, and PS. Despite abundant evidence, most radiation oncologists continue to prescribe multifraction schedules for patients who fit the eligibility criteria of previous randomized controlled trials. The results confirmed a delay in the incorporation of evidence into practice for palliative RT for painful bone metastases.	4

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
14. 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.	Experimental-Tx	455 patients in the 8 Gy arm; 443 in the 30 Gy arm	Prospective phase III randomized trial to evaluate palliative RT conducted for patients with breast or prostate cancer who had one to three sites of painful bone metastases and moderate to severe pain.	Grade 2-4 acute toxicity was more frequent in the 30 Gy arm (17%) than in the 8 Gy arm (10%) (Difference = 7%, 95% CI, 3% to 12%; P=.002). Late toxicity was rare (4%) in both arms. The overall response rate was 66%. CR and PR rates were 15% and 50%, respectively, in the 8 Gy arm compared with 18% and 48% in the 30 Gy arm (P=.6). At 3 months, 33% of all patients no longer required narcotic medications. The incidence of subsequent pathologic fracture was 5% for the 8 Gy arm and 4% for the 30 Gy arm. The retreatment rate was statistically significantly higher in the 8 Gy arm (18%) than in the 30 Gy arm (9%) (P<.001). Both regimens were equivalent in terms of pain and narcotic relief at 3 months and were well tolerated with few adverse effects. The 8 Gy arm had a higher rate of re-treatment but had less acute toxicity than the 30 Gy arm.	1

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
15. Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. *Cochrane Database Syst Rev.* 2012;2:CD003474.	Review/Other-Tx	34 randomized control trials	To assess the effect of bisphosphonates on SREs, bone pain, QoL, recurrence and survival in women with breast cancer with bone metastases, advanced breast cancer without clinical evidence of bone metastases and early breast cancer and to assess the effect of denosumab on SREs, bone pain and QoL in women with breast cancer with bone metastases.	In 9 studies (2,806 patients with breast cancer with bone metastases), comparing bisphosphonates with placebo or no bisphosphonates, bisphosphonates reduced the SREs risk by 15% (RR 0.85; 95% CI, 0.77–0.94; P=0.001). This benefit was most certain with intravenous zoledronic acid (4 mg) (RR 0.59; 95% CI, 0.42–0.82); pamidronate (90 mg) (RR 0.77; 95% CI, 0.69–0.87); and ibandronate (RR 0.80; 95% CI, 0.67–0.96). A direct comparison of zoledronic acid and pamidronate confirmed at least equivalent efficacy in a single large study. In 3 studies (3,405 patients with breast cancer with bone metastases), compared with bisphosphonates, subcutaneous denosumab was more effective in reducing the risk of SREs (RR 0.78; 95% CI, 0.72–0.85; P<0.00001). Bisphosphonates reduced the SRE rate in 12 studies (median reduction 28%, range 14% to 48%), with statistically significant reductions reported in 10 studies. Bisphosphonates in women with advanced breast cancer without clinically evident bone metastases did not reduce the incidence of bone metastases, or improve survival in 3 studies (320 patients). In 7 studies (7,847 patients with early breast cancer), currently there is no evidence supporting bisphosphonates in reducing the incidence of bone metastases compared to no bisphosphonates (RR 0.94; 95% CI, 0.82–1.07; P=0.36). In 3 studies (2,190 patients with early breast cancer), early bisphosphonate treatment also did not significantly reduce the incidence of bone metastases compared to delayed bisphosphonate treatment (RR 0.73; 95% CI, 0.40–1.33; P=0.31).	4

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
16. Van Poznak CH, Temin S, Yee GC, et al. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. *J Clin Oncol.* 2011;29(9):1221-1227.	Review/Other-Tx	N/A	To update the recommendations on the role of bone-modifying agents in the prevention and treatment of SREs for patients with metastatic breast cancer with bone metastases.	Bone-modifying agent therapy is only recommended for patients with breast cancer with evidence of bone metastases; denosumab 120 mg subcutaneously every 4 weeks, intravenous pamidronate 90 mg over no less than 2 hours, or zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks is recommended. There is insufficient evidence to demonstrate greater efficacy of one bone-modifying agent over another. In patients with a calculated serum creatinine clearance of more than 60 mg/min, no change in dosage, infusion time, or interval of bisphosphonate administration is required. Serum creatinine should be monitored before each dose. All patients should receive a dental examination and appropriate preventive dentistry before bone-modifying agent therapy and maintain optimal oral health. Current standards of care for cancer bone pain management should be applied at the onset of pain, in concert with the initiation of bone-modifying agent therapy. The use of biochemical markers to monitor bone-modifying agent use is not recommended.	4
17. Chow E, Hoskin PJ, Wu J, et al. A phase III international randomised trial comparing single with multiple fractions for re-irradiation of painful bone metastases: National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) SC 20. *Clin Oncol (R Coll Radiol).* 2006;18(2):125-128.	Review/Other-Tx	N/A	To review randomized trials which compare single with multiple fractions for re-irradiation of painful bone metastases.	Many patients with relapsed pain or poor response to initial radiation may be lost to follow-up or may not be referred back to the radiation oncologist for consideration of re-irradiation. The response to re-irradiation in the published reports is variable, and no consistent policy for dose fractionation is followed or recommended.	4

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
18. van der Linden YM, Lok JJ, Steenland E, et al. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. *Int J Radiat Oncol Biol Phys.* 2004;59(2):528-537.	Experimental-Tx	1,157 patients: 579 patients received single fractions of 8 Gy; 578 patients received 6 fractions of 4 Gy	Randomized trial to evaluate factors influencing retreatment and its effect on response.	Response to initial treatment was 71% after single fractions vs 73% after multiple fractions (P=0.84). Retreatment raised response to 75% for single fractions; multiple fractions remained unaltered (P=0.54). The response status after initial treatment did not predict occurrence of retreatment: 35% single fractions vs 8% multiple fractions nonresponders and 22% single fractions vs 10% multiple fractions patients with progressive pain were retreated. Logistic regression analyses showed the randomization arm and the pain score before retreatment to significantly predict retreatment (P<0.001). Retreatment for nonresponders was successful in 66% single fractions vs 33% multiple fractions patients (P=0.13). Retreatment for progression was successful in 70% single fractions vs 57% multiple fractions patients (P=0.24). With or without the effect of retreatment, single fractions and multiple fractions RT provided equal palliation for painful bone metastases. Irrespective of response to initial treatment, physicians were more willing to retreat after a single fraction. Overall, retreatment was effective in 63% of retreated patients.	1
19. Huisman M, van den Bosch MA, Wijlemans JW, van Vulpen M, van der Linden YM, Verkooijen HM. Effectiveness of reirradiation for painful bone metastases: a systematic review and meta-analysis. *Int J Radiat Oncol Biol Phys.* 2012;84(1):8-14.	Review/Other-Tx	10 articles for systematic review and 7 articles for the meta-analysis	A systematic review and meta-analysis to quantify the effectiveness of reirradiation for achieving pain control in patients with painful bone metastases.	Overall study quality was mediocre. Of the 2,694 patients initially treated for metastatic bone pain, 527 (20%) patients underwent reirradiation. Overall, a pain response after reirradiation was achieved in 58% of patients (pooled overall response rate 0.58, 95% CI, 0.49–0.67). There was a substantial between-study heterogeneity (I(2) = 63.3%, P=0.01) because of clinical and methodological differences between studies.	4

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
20. Chow E, Van Der Linden Y, Roos D, et al. Response and Quality of Life (QOL) Outcomes in a Randomized Trial of Single Versus Multiple Fractions (Fx) for Re-irradiation (RE-RT) of Painful Bone Metastases (PBM): NCIC CTG SC.20. *Int J Radiat Oncol Biol Phys.* 2013;87(2):S6.	Observational-Tx	850 patients	To assess the optimal re-irradiation RT dose fractionation schedule and the QoL changes for painful bone metastases.	Between 01/2004 and 06/2012, 850 patients from 9 countries were enrolled. Most common cancers were prostate (27%), breast (26%) and lung (22%). Before the 2 month assessment, 98 (11%) patients died. By intention to treat, the 2-month RR was available in 66% (557/850) and was 119/425 (28%) with 8 Gy and 136/425 (32%) with 20 Gy (P=0.2); the upper boundary of the 95% CI for RR difference = 9.2% and is less than the pre-specified NI margin. By per-protocol analysis, 2-month RR was available in 521 and was 117/258 (45.3%) with 8 Gy and 135/263 (51.3%) with 20 Gy (P=0.17); the upper boundary of the 95% CI for RR difference = 13.2%, which exceeds 10% non-inferiority boundary. Day 14 adverse events differing by treatment were: lack of appetite (P=0.01), vomiting (P=0.001), diarrhea (P=0.02) and skin reddening (P=0.002); all were worse with 20 Gy. There were 30 vs 20 pathological fractures and 7 vs 2 spinal cord compressions with 8 Gy and 20 Gy, respectively (P=NS). In the 664 patients enrolled in monthly QoL assessments, compliance rates varied between 74% and 87% over the first 6 months. At 2 months, the mean scores of pain and sleep items were improved. The pain item was improved in each of the 6 assessments in both arms. About 50% of patients reported better scores at 6 months in role, cognitive, social and global domains and in the fatigue, pain, and sleep items. No significant differences in QoL scores were detected between arms.	1

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
21. Chow E, van der Linden YM, Roos D, et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. *Lancet Oncol.* 2014;15(2):164-171.	Experimental-Tx	521 total patients	To assess two dose fractionation schedules in patients with painful bone metastases needing repeat radiation therapy.	Between Jan 7, 2004, and May 24, 2012, we randomly assigned 425 patients to each treatment group. 19 (4%) patients in the 8 Gy group and 12 (3%) in the 20 Gy group were found to be ineligible after randomization, and 140 (33%) and 132 (31%) patients, respectively, were not assessable at 2 months and were counted as missing data in the intention-to-treat analysis. In the intention-to-treat population, 118 (28%) patients allocated to 8 Gy treatment and 135 (32%) allocated to 20 Gy treatment had an overall pain response to treatment (P=0.21; response difference of 4.00% [upper limit of the 95% CI 9.2, less than the prespecified noninferiority margin of 10%]). In the per-protocol population, 116 (45%) of 258 patients and 134 (51%) of 263 patients, respectively, had an overall pain response to treatment (P=0.17; response difference 6.00% [upper limit of the 95% CI 13.2, greater than the prespecified noninferiority margin of 10%]). The most frequently reported acute radiation-related toxicities at 14 days were lack of appetite (201 [56%] of 358 assessable patients who received 8 Gy vs 229 [66%] of 349 assessable patients who received 20 Gy; P=0.011) and diarrhea (81 [23%] of 357 vs 108 [31%] of 349; P=0.018). Pathological fractures occurred in 30 (7%) of 425 patients assigned to 8 Gy and 20 (5%) of 425 assigned to 20 Gy (odds ratio 1.54, 95% CI, 0.85–2.75; P=0.15), and spinal cord or cauda equina compressions were reported in 7 (2%) of 425 vs 2 (<1%) of 425, respectively (odds ratio 3.54, 95% CI, 0.73–17.15; P=0.094).	1

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
22. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer*. 2012;48(16):3082-3092.	Review/Other-Tx	5,723 total patients from 3 trials	To evaluate the efficacy and safety of denosumab vs zoledronic acid across 3 pivotal studies.	Denosumab was superior to zoledronic acid in delaying time to first on-study SRE by a median 8.21months, reducing the risk of a first SRE by 17% (HR, 0.83 [95% CI: 0.76–0.90]; $P<0.001$). Efficacy was demonstrated for first and multiple events and across patient subgroups (prior SRE status; age). Disease progression and overall survival were similar between the treatments. In contrast to zoledronic acid, denosumab did not require monitoring or dose modification/withholding based on renal status, and was not associated with acute-phase reactions. Hypocalcaemia was more common for denosumab. Osteonecrosis of the jaw occurred at a similar rate ($P=0.13$).	4
23. Bishr M, Saad F. Overview of the latest treatments for castration-resistant prostate cancer. *Nat Rev Urol*. 2013;10(9):522-528.	Review/Other-Tx	N/A	To provide an overview of therapeutic options for castration-resistant prostate cancer.	4 new agents (cabazitaxel, abiraterone acetate, enzalutamide, and radium-233) have been shown to prolong overall survival in patients with castration-resistant prostate cancer in the postchemotherapy setting. Targeting the androgen receptor pathway continues to have an important role in the treatment of castration-resistant prostate cancer, with abiraterone acetate and enzalutamide being the most exciting developments. Cabazitaxel is now considered the standard-of-care second-line chemotherapy for men with metastatic castration-resistant prostate cancer. Bone-targeted therapy is an active area of research, with denosumab being the first bone-targeted agent able to significantly delay the appearance of bone metastases in patients with castration-resistant prostate cancer and radium-223 being the first radiopharmaceutical agent to improve survival in patients with metastatic castration-resistant prostate cancer.	4

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
24. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med.* 2013;368(2):138-148.	Experimental-Tx	1,088 patients	To evaluate the effects of abiraterone plus prednisone on radiographic progression free survival, overall survival, increase in pain, and clinically relevant measures of disease progression in patients with progressive metastatic castration-resistant prostate cancer who had not received chemotherapy and in whom clinically significant cancer-related symptoms had not developed.	The study was unblinded after a planned interim analysis that was performed after 43% of the expected deaths had occurred. The median radiographic progression-free survival was 16.5 months with abiraterone-prednisone and 8.3 months with prednisone alone (HR for abiraterone-prednisone vs prednisone alone, 0.53; 95% CI, 0.45 to 0.62; $P<0.001$). Over a median follow-up period of 22.2 months, overall survival was improved with abiraterone-prednisone (median not reached, vs 27.2 months for prednisone alone; HR, 0.75; 95% CI, 0.61 to 0.93; $P=0.01$) but did not cross the efficacy boundary. Abiraterone-prednisone showed superiority over prednisone alone with respect to time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, prostate-specific antigen progression, and decline in PS. Grade 3 or 4 mineralocorticoid-related adverse events and abnormalities on liver-function testing were more common with abiraterone-prednisone.	1
25. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. Version 1.2014. 2014; Available at: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed February 28, 2014.	Review/Other-Tx	N/A	NCCN guidelines on prostate cancer.	No results stated in abstract.	4
26. Pinto A. Cabozantinib: a novel agent with a dual mechanism of action for castration-resistant prostate carcinoma. *Cancer Chemother Pharmacol.* 2014;73(2):219-222.	Review/Other-Tx	N/A	To review the clinical development of cabozantinib in prostate cancer and future research possibilities for this drug.	No results stated in abstract.	4

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
27. Baczyk M, Czepczynski R, Milecki P, Pisarek M, Oleksa R, Sowinski J. 89Sr versus 153Sm-EDTMP: comparison of treatment efficacy of painful bone metastases in prostate and breast carcinoma. *Nucl Med Commun.* 2007;28(4):245-250.	Observational-Tx	100 patients	To compare the analgesic effect of radionuclide therapy using Sr and Sm-EDTMP in patients with painful bone metastases of these tumors.	Complete pain relief was found in 40% of women and 40% of men treated using Sm-EDTMP and in 25% of women and 33% of men treated with Sr. No analgesic effect occurred in 20% of patients. A better analgesic effect was found in cases of osteoblastic metastases compared to mixed metastases. Statistically significant reduction of pain intensity, use of analgesic drugs and improvement of performance in Karnofsky scale was found in cases of both radionuclides.	1
28. Dolezal J, Vizda J, Odrazka K. Prospective evaluation of samarium-153-EDTMP radionuclide treatment for bone metastases in patients with hormone-refractory prostate cancer. *Urol Int.* 2007;78(1):50-57.	Observational-Tx	32 men	To assess the efficacy of (153)Sm-EDTMP therapy.	Significant pain relief was observed in 44% and 38% of patients, mild relief in 31% and 34% and no effect in 25% and 28% of patients, 1 and 3 months after administration, respectively. Pain palliation was accompanied by an improvement in mobility and a decrease in necessary dosage of analgesics. Mild and transient bone marrow suppression was observed as a side effect of (153)Sm-EDTMP treatment. None of the patients showed hematological toxicity grade 4, and only 2 showed grade 3 (NCI CTC). The majority of the patients had hematological toxicity grade 1 or 2.	1
29. Sartor O, Reid RH, Hoskin PJ, et al. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology*. 2004;63(5):940-945.	Experimental-Tx	152 men	A phase III randomized trial was designed to assess the effectiveness of samarium-153 (153Sm)-lexidronam for palliation of bone pain in patients with hormone-refractory prostate cancer.	153Sm-lexidronam had positive effects on measures of pain relief compared with placebo within 1 to 2 weeks. Reductions in opioid use were recorded at weeks 3 and 4. Because nonresponders were unblinded at week 4, statistical comparisons between the arms beyond week 4 were not possible. Mild, transient bone marrow suppression was the only adverse event associated with 153Sm-lexidronam administration. The mean nadir white blood cell and platelet count (3 to 4 weeks after treatment) was 3800/microL and 127,000/microL, respectively. Counts recovered to baseline after approximately 8 weeks. No grade 4 decreases in either platelets or white bloods cells were documented.	1

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. Schild SE. Role of radiation therapy in the treatment of melanoma. *Expert Rev Anticancer Ther*. 2009;9(5):583-586.	Review/Other-Tx	N/A	To review the role of RT in the treatment of melanoma.	The use of RT requires careful planning resulting in the administration of a tumoricidal dose to the tumor cells with adequate sparing of normal tissues. RT has been used for primary therapy, postresection adjuvant therapy and palliation of symptomatic melanoma. Curative RT has been given for uveal melanoma yielding patient survival equivalent to enucleation. RT has been administered to patients with unresectable disease yielding relatively favorable results. As an adjuvant therapy postoperatively, RT has been used selectively to improve local disease control. RT is used successfully as a palliative maneuver for symptoms related to distant metastatic melanoma in patients with incurable disease.	4
31. Strojan P. Role of radiotherapy in melanoma management. *Radiol Oncol.* 2010;44(1):1-12.	Review/Other-Tx	N/A	To review radiobiological properties of melanoma that govern the decisions for the fractionation patterns used in the treatment of this disease and the indications for irradiation and the results of pertinent clinical studies from the literature with a brief description of RT techniques.	Basic treatment modality in melanoma is surgery. However, whenever surgery is not radical or there are adverse prognostic factors identified on histopathological examination of resected tissue specimen, it needs to be supplemented. Also, in patients with unresectable disease or in those not being suitable for major surgery or who refuse proposed surgical intervention, other effective mode(s) of therapy need to be implemented. From this perspective, supported by clinical experiences and literature results, RT is a valuable option: it is effective and safe, in curative and palliative setting.	4

Non-Spine Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Lutz S, Spence C, Chow E, Janjan N, Connor S. Survey on use of palliative radiotherapy in hospice care. *J Clin Oncol.* 2004;22(17):3581-3586.	Review/Other-Tx	480 facilities	To survey hospice professionals to assess the perceived need for palliative RT in the hospice setting, investigate factors that limit the access of hospice patients to RT, and to suggest areas of future collaboration on education, research, and patient advocacy.	The findings suggest that the majority of hospice professionals feel that RT is important in palliative oncology and that RT is widely available in the United States. Yet, less than 3% on average of hospice patients served by hospices responding to the survey actually received RT in 2002. The most common barriers to RT in hospice care include RT expense, transportation difficulties, short life expectancy, and educational deficiencies between the specialties. Multiple barriers act to limit the use of palliative RT in hospice care. Finding ways to surmount these obstacles will provide opportunity for improvement in the end-of-life care of cancer patients.	4
33. Hird A, Chow E, Zhang L, et al. Determining the incidence of pain flare following palliative radiotherapy for symptomatic bone metastases: results from three canadian cancer centers. *Int J Radiat Oncol Biol Phys.* 2009;75(1):193-197.	Review/Other-Tx	111 total patients	To determine the incidence of pain flare following RT for painful bone metastases.	The overall pain flare incidence was 44/111 (40%) during RT and within 10 days following the completion of RT. Patients treated with a single 8 Gy reported a pain flare incidence of 39% (27/70) and, with multiple fractions, 41% (17/41). More than one third of the enrolled patients experienced a pain flare. Identifying at-risk individuals and managing potential pain flares is crucial to achieve an optimal level of care.	4

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

CI = Confidence interval

CR = Complete response

EBRT = External-beam radiation therapy

EDTMP = Ethylene-diamino-tetramethylene-phosphonate

HR = Hazard ratio

PR = Partial response

PS = Performance status

QoL = Quality of Life

RR = Risk ratio

RT = Radiation therapy

SBRT = Stereotactic body radiotherapy

SREs= Skeletal-related events