Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. Fisher CG, DiPaola CP, Ryken TC, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine (Phila Pa 1976)* 2010; 35(22):E1221-1229.	7	N/A	To use an evidence-based medicine process using the best available literature and expert opinion consensus to develop a comprehensive classification system to diagnose neoplastic spinal instability.	The Spine Instability Neoplastic Score is a comprehensive classification system with content validity that can guide clinicians in identifying when patients with neoplastic disease of the spine may benefit from surgical consultation. It can also aid surgeons in assessing the key components of spinal instability due to neoplasia and may become a prognostic tool for surgical decision-making when put in context with other key elements such as neurologic symptoms, extent of disease, prognosis, patient health factors, oncologic subtype, and radiosensitivity of the tumor.	4
2. 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.	15	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.	3

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
3. 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.	7 (systematic review)	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.	2

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
4. 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.	15	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.	3

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
5. 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 24 June 2011.	15	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

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
6. Lo SS, Sahgal A, Wang JZ, et al. Stereotactic body radiation therapy for spinal metastases. *Discov Med* 2010; 9(47):289-296.	7	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.	3
7. Ryu S, Rock J, Jain R, et al. Radiosurgical decompression of metastatic epidural compression. *Cancer* 2010; 116(9):2250-2257.	3a	62 patients	To quantitatively determine the degree of epidural decompression by radiosurgery of metastatic epidural compression.	The mean epidural tumor volume reduction was 65 +/- 14% at 2 months after radiosurgery. The epidural tumor area at the level of the most severe spinal cord compression was 0.82 +/- 0.08 cm(2) before radiosurgery and 0.41 +/- 0.06 cm(2) after radiosurgery (P<.001). The cal sac patency improved from 55 +/- 4% to 76 +/- 3% (P<.001). Overall, neurological function improved in 81%. This study demonstrated a radiosurgical decompression of epidural tumor. Although neurosurgical decompression and RT is the standard treatment in patients with good performance, radiosurgical decompression can be a viable noninvasive treatment option for malignant epidural compression.	2

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
8. Sahgal A, Larson DA, Chang EL. Stereotactic body radiosurgery for spinal metastases: a critical review. *Int J Radiat Oncol Biol Phys* 2008; 71(3):652-665.	7	29 reports of stereotactic body radiosurgery	To review the current status of stereotactic body radiosurgery for spinal metastases with respect to its apparatus, clinical indications, outcomes and techniques, and spinal cord tolerance.	The field of spinal stereotactic body radiosurgery is in its formative years. Studies from a limited number of centers suggest that SBRS used in the treatment of spinal metastases appears to be safe and effective both in terms of radiographic tumor control and pain relief. This is particularly important as a viable noninvasive option for the previously irradiated patient with painful spinal metastases, as these patients have not had many noninvasive therapeutic options available in the past.	4
9. Shiue K, Sahgal A, Chow E, et al. Management of metastatic spinal cord compression. *Expert Rev Anticancer Ther* 2010; 10(5):697-708.	7	N/A	To review the management of metastatic spinal cord compression.	Once spinal cord compression is suspected, diagnostic imaging of the spine should be obtained to confirm diagnosis. Treatment consists of surgery, RT or a combination of both. SBRT has also been incorporated into the management of spinal cord compression. The treatment decision should be made based on multiple factors, including tumor histology, retropulsion of bony fragments, PS of the patient and status of extraspinal systemic disease. This review focuses on the pathophysiology, diagnosis and management of spinal cord compression.	4

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
10. Ibrahim A, Crockard A, Antonietti P, et al. Does spinal surgery improve the quality of life for those with extradural (spinal) osseous metastases? An international multicenter prospective observational study of 223 patients. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2007. *J Neurosurg Spine* 2008; 8(3):271-278.	3a	223 patients	To determine if surgery improves the quality of remaining life in patients with spinal metastatic and tumor-related systemic disease.	The mean patient age was 61 years. Patients presented with pain in 92% of cases, paraparesis in 24%, and abnormal urinary sphincter function in 22% (5% were incontinent). Breast, renal, lung, and prostate accounted for 65% of the cancers, and in 60% of patients there were widespread spinal metastases (Tomita Type 6 or 7). The incidence of perioperative death (within 30 days of surgery) was 5.8%. Postoperatively 71% of the entire group had improved pain control, 53% regained or maintained their independent mobility, and 39% regained urinary sphincter function. The median survival for the cohort was 352 days (11.7 months); those who underwent excision survived significantly longer than those in the palliative group (P=0.003). As with survival results, functional improvement outcome was better in those who underwent excision. Surgical treatment was effective in improving quality of life by providing better pain control, enabling patients to regain or maintain mobility, and offering improved sphincter control. Although not a treatment of the systemic cancer, surgery is feasible, has acceptably low mortality and morbidity rates, and for many will improve the quality of their remaining life.	2

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
11. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet* 2005; 366(9486):643-648.	1	101 total patients surgery followed by RT (n=50) or RT alone (n=51)	Randomized, multi-institutional, non-blinded trial to assess the efficacy of direct decompressive surgery.	Significantly more patients in the surgery group (42/50, 84%) than in the RT group (29/51, 57%) were able to walk after treatment (odds ratio 6.2 [95% CI 2.0-19.8] P=0.001). Patients treated with surgery also retained the ability to walk significantly longer than did those with RT alone (median 122 days vs 13 days, P=0.003). 32 patients entered the study unable to walk; significantly more patients in the surgery group regained the ability to walk than patients in the radiation group (10/16 [62%] vs 3/16 [19%], P=0.01). The need for corticosteroids and opioid analgesics was significantly reduced in the surgical group. Direct decompressive surgery plus postoperative RT is superior to treatment with RT alone for patients with spinal cord compression caused by metastatic cancer.	1

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
12. Prewett S, Venkitaraman R. Metastatic spinal cord compression: review of the evidence for a radiotherapy dose fractionation schedule. *Clin Oncol (R Coll Radiol)* 2010; 22(3):222-230.	7	N/A	To review and evaluate the evidence base for the RT dose for spinal cord compression.	Although no definitive prospective randomized trial data have been produced to clarify the role of the most appropriate RT dose fractionation schedules in all patient subgroups, there are inferences that can be made from the studies undertaken so far. Long-course RT with doses of 30 Gy in 10 fractions or more seems to offer no benefit compared with shorter regimens in terms of immediate neurological outcome or survival, but results in improved local control and less in-field recurrences, which would be an advantage in patient groups expected to live longer. Shorter courses are more cost-effective, less time-consuming and could be considered for patients with extensive metastatic disease, a life expectancy of > 6 months and for primary tumors such as lung, melanoma and sarcoma, which are less radiosensitive. In this unfavorable group of patients, the optimal dose would be just a single 8 Gy dose, as it has been shown to provide equivalent functional recovery, local control and survival compared with longer schedules. In patients with a good prognosis, with an expected survival of over 6 months, in favorable malignancies such as myeloma, breast and prostate cancer, with no visceral metastasis and in the postoperative setting, 30 Gy in 10 fractions should on balance be the recommended regimen of choice above the widely adopted 20 Gy in 5 fractions. There seems to be no practical advantage in offering treatments greater or longer than 30 Gy in 10 fractions in any patient subgroup.	4

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
13. Jin R, Rock J, Jin JY, et al. Single fraction spine radiosurgery for myeloma epidural spinal cord compression. *J Exp Ther Oncol* 2009; 8(1):35-41.	4	24 patients 31 lesions	To determine the role of single fraction radiosurgery for epidural spinal cord compression due to multiple myeloma.	Median follow-up was 11.2 months (range 1-55). Primary endpoints of this study were pain control, neurological improvement, and radiographic tumor control. Overall pain control rate was 86%; complete relief in 54%, and partial relief in 32% of the patients. Seven patients presented with neurological deficits. Five patients neurologically improved or became normal after radiosurgery. Complete radiographic response of the epidural tumor was noted in 81% at 3 months after radiosurgery. During the follow-up time, there was no radiographic or neurological progression at the treated spine. The treatment was noninvasive and well tolerated. Single fraction radiosurgery achieved an excellent clinical and radiographic response of myeloma epidural spinal cord compression. Radiosurgery can be a viable treatment option for myeloma epidural compression.	2
14. 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.	15	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

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
15. Maranzano E, Bellavita R, Rossi R, et al. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. J Clin Oncol 2005; 23(15):3358-3365.	1	276 patients: 142 treated with the short course, 134 treated with the split course	Randomized trial to assess the clinical outcome and toxicity of two different hypofractionated RT regimens in metastatic spinal cord compression.	A total of 276 (92%) patients were assessable; 142 (51%) treated with the short-course and134 (49%) treated with the split-course RT regimen. There was no significant difference in response, duration of response, survival, or toxicity found between the two arms. When short- vs split-course regimens were compared, after RT 56% and 59% patients had back pain relief, 68% and 71% were able to walk, and 90% and 89% had good bladder function, respectively. Median survival was 4 months and median duration of improvement was 3.5 months for both arms. Toxicity was equally distributed between the two arms: grade 3 esophagitis or pharyngitis was registered in 4 patients (1.5%), grade 3 diarrhea occurred in 4 patients (1.5%), and grade 3 vomiting or nausea occurred in 10 patients (6%). Late toxicity was never recorded.	1
16. Maranzano E, Trippa F, Casale M, et al. 8Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. Radiother Oncol 2009; 93(2):174-179.	1	303 patients: 150 treated with short course, 153 treated with the single-dose RT	Randomized phase III equivalence trial to determine whether in metastatic spinal cord compression patients 8 Gy single-dose is as effective as 8 Gy x 2 with regard to symptom control, duration of response, survival and toxicity.	No difference in response was found between the two RT schedules adopted. Median duration of response was 5 and 4.5 months for short-course and single-dose RT (P=0.4), respectively. The median overall survival was 4 months for all cases. Light acute toxicity was registered in a minority of cases. Late toxicity was never recorded.	1

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
17. Rades D, Lange M, Veninga T, et al. Final results of a prospective study comparing the local control of short-course and long-course radiotherapy for metastatic spinal cord compression. Int J Radiat Oncol Biol Phys 2011; 79(2):524-530.	2	265: 31 short course, 134 long course	The primary goal was to compare local control from short-course (1 x 8 Gy/5 x 4 Gy) and long-course RT (10 x 3 Gy/15 x 2.5 Gy/20 x 2 Gy). Secondary end points were motor function and survival. The analysis of local control (no metastatic spinal cord compression recurrence in the irradiated spinal area) included the 224 patients with improvement or no change of motor deficits during RT. Eleven additional factors were evaluated for outcomes.	1-year local control was 61% after short course and 81% after long-course RT (P=0.005). On multivariate analysis, improved local control was associated with long-course RT (P=0.018). Motor function improved in 37% after short-course and 39% after long-course RT (p = 0.95). Improved motor function was associated with better PS (P=0.015), favorable tumor type (P=0.034), and slower development of motor deficits (P<0.001). 1-year survival rates were 23% after short-course and 30% after long-course RT (P=0.28). On multivariate analysis, improved survival was associated with better PS (P<0.001), no visceral metastases (P<0.001), involvement of only one to three vertebrae (P=0.040), ambulatory status (P=0.038), and bisphosphonate administration after RT (P<0.001).	2
18. Lo SS, Sahgal A, Hartsell WF, et al. The treatment of bone metastasis with highly conformal radiation therapy: a brave new world or a costly mistake? *Clin Oncol (R Coll Radiol)* 2009; 21(9):662-664.	7	N/A	To evaluate the treatment of bone metastasis with highly conformal RT.	At present, the use of highly conformal therapy is between a brave new world and a costly mistake. The small but growing body of outcome data from mostly retrospective and a few prospective studies may help define its value and selected indications, but its common use outside of those arenas will continue to be seen as excessive and costly. Utilization of highly conformal techniques may be justified in critical sites like the spine where progression can ultimately lead to greater cost to the system and patient. But in clinical scenarios where there is diffuse metastasis or the patient's PS is very poor and short survival is expected, the use of highly conformal techniques is extremely unlikely to confer additional benefits compared to the use of conventional RT.	4

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
19. Azzoli CG, Temin S, Aliff T, et al. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. *J Clin Oncol* 2011; 29(28):3825-3831.	15	N/A	Update of one recommendation of the ASCO Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer (NSCLC) regarding switch maintenance chemotherapy.	In patients with stage IV non-small-cell lung cancer, first-line cytotoxic chemotherapy should be stopped at disease progression or after 4 cycles in patients whose disease is stable but not responding to treatment. Two-drug cytotoxic combinations should be administered for no more than 6 cycles. For those with stable disease or response after 4 cycles, immediate treatment with an alternative, single-agent chemotherapy such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients, or erlotinib in unselected patients may be considered.	4
20. Schnipper LE, Smith TJ, Raghavan D, et al. American society of clinical oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. *J Clin Oncol* 2012; 30(14):1715-1724.	15	N/A	To identify the "top five" list: Practices and interventions that are costly, widely used, and not supported by high-level clinical evidence; created by the Cost of Care Task Force and reviewed/supported by over 200 clinical oncologists.	1. Do not use cancer-directed therapy for patients with solid tumors who have the following characteristics: low PS (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and with no strong evidence supporting the clinical value of further anticancer treatment. 2. Do not perform PET, CT, and radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis. 3. Do not perform PET, CT, and radionuclide bone scans in the staging of early breast cancer at low risk for metastasis. 4. Do not perform surveillance testing (biomarkers) or imaging (PET, CT, and radionuclide bone scans) for asymptomatic patients who have been treated for breast cancer with curative intent. 5. Do not use white cell–stimulating factors for primary prevention of febrile neutropenia for patients with less than 20% risk for this complication.	4

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
21. 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.	15	N/A	To update the recommendations on the role of bone-modifying agents in the prevention and treatment of skeletal-related events 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
22. Santen RJ. Clinical review: Effect of endocrine therapies on bone in breast cancer patients. *J Clin Endocrinol Metab* 2011; 96(2):308-319.	7	N/A	To review the literature to determine the mechanistic effects of estrogen on bone and clinical data regarding bone density, bone turnover markers, and fracture rates in women with breast cancer taking tamoxifen or aromatase inhibitors.	Tamoxifen increases bone density and reduces fractures in postmenopausal women with breast cancer, whereas aromatase inhibitors increase rate of fracture, accelerate loss of bone mineral density, and enhance levels of markers of bone formation and resorption. Bisphosphonates and denosumab counteract the effects of the aromatase inhibitors on bone. Endocrine therapy for postmenopausal women with breast cancer exerts substantial effects on bone, and guidelines are available to assist in the management of bone-related problems.	4

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
23. Mhaskar R, Redzepovic J, Wheatley K, et al. Bisphosphonates in multiple myeloma. *Cochrane Database Syst Rev* 2010; (3):CD003188.	7	1,520 patients from 17 trials analyzed with bisphosphonates; 1,490 analyzed in control groups	To analyze observational studies targeting osteonecrosis of jaw.	In comparison with placebo/no treatment, the pooled analysis demonstrated the beneficial effect of bisphosphonates on prevention of pathological vertebral fractures (RR=0.74 (95% CI: 0.62 to 0.89), P=0.001), total skeletal related events (RR=0.80 (95% CI: 0.72 to 0.89), P<0.0001) and on amelioration of pain (RR=0.75 (95% CI: 0.60 to 0.95), P=0.01). No significant effect of bisphosphonates on overall survival, progression-free survival, hypercalcemia or on the reduction of non-vertebral fractures. The indirect meta-analyses did not find the superiority of any particular type of bisphosphonate over others. Adding bisphosphonates to the treatment of multiple myeloma reduces pathological vertebral fractures, skeletal related events and pain but not mortality. Assuming the baseline risk of 20% to 50% for vertebral fracture without treatment, it is estimated that between 8 and 20 multiple myeloma patients should be treated to prevent vertebral fracture(s) one patient. Assuming the baseline risk of 31% to 76% for pain amelioration without treatment, it is estimated that between 5 to 13 multiple myeloma patients should be treated to reduce pain in one patient. Also, with the baseline risk of 35% to 86% for skeletal related events without treatment, it is estimated that between 6 and 15 multiple myeloma patients should be treated to prevent skeletal related event(s) in one patient. No bisphosphonate appears to be superior to others.	2

Spinal Bone Metastases
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
24. Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. *Lancet Oncol* 2011; 12(3):225-235.	1	134 patients randomized to kyphoplasty (n=70) or non-surgical management (n=64)	Randomized, multicenter trial to assess the efficacy and safety of balloon kyphoplasty compared with non-surgical management for patients with cancer who have painful vertebral compression fractures.	65 patients in the kyphoplasty group and 52 in the control group had data available at 1 month. The mean Roland-Morris disability questionnaire score in the kyphoplasty group changed from 17.6 at baseline to 9.1 at 1 month (mean change -8.3 points, 95% CI; -6.4 to -10.2; P<0·0001). The mean score in the control group changed from 18.2 to 18.0 (mean change 0.1 points; 95% CI; -0.8 to 1.0; P=0·83). At 1 month, the kyphoplasty treatment effect for Roland-Morris disability questionnaire was -8.4 points (95% CI: -7.6 to -9.2; P<0·0001). The most common adverse events within the first month were back pain (4/70 in the kyphoplasty group and 5/64 in the control group) and symptomatic vertebral fracture (two and three, respectively). One patient in the kyphoplasty group had an intraoperative non-Q-wave myocardial infarction, which resolved and was attributed to anesthesia. Another patient in this group had a new vertebral compression fracture, which was thought to be device related. For painful vertebral compression fractures in patients with cancer, kyphoplasty is an effective and safe treatment that rapidly reduces pain and improves function.	1

Spinal Bone Metastases
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
25. Dispenzieri A, Wiseman GA, Lacy MQ, et al. A Phase II study of (153)Sm-EDTMP and high-dose melphalan as a peripheral blood stem cell conditioning regimen in patients with multiple myeloma. *Am J Hematol* 2010; 85(6):409-413.	3c	46 patients with newly diagnosed or relapsed disease compared to 102 patients contemporaneously treated with high-dose melphalan and autologous hematopoietic stem cell support	Phase 11 study was performed to combine (153)Samarium ethylenediaminetetramethylenephosphonate, a radiopharmaceutical approved for the palliation of pain caused by metastatic bone lesions, high-dose melphalan and autologous hematopoietic stem cell support.	59% of study patients achieved a very good PR or better. With a median follow-up of 7.1 years, the median overall survival and progression free survival from study registration was 6.2 years (95% CI; 4.6-7.5 years) and 1.5 years (1.1-2.2 years), respectively, which compared favorably to contemporaneously treated non-study patients. Addition of high-dose (153)Samarium ethylenediaminetetramethylenephosphonate to melphalan conditioning appears to be safe, well tolerated, and worthy of further study in the context of novel agents and in the Phase III setting.	2
26. Papanastassiou ID, Phillips FM, Van Meirhaeghe J, et al. Comparing effects of kyphoplasty, vertebroplasty, and non-surgical management in a systematic review of randomized and non-randomized controlled studies. *Eur Spine J* 2012:[E-pub ahead of print].	7 (meta-analysis)	27 articles	To determine through a systematic review if differences in safety or efficacy exist between balloon kyphoplasty, vertebroplasty and non-surgical management for the treatment of osteoporotic vertebral compression fractures.	Pain reduction in both balloon kyphoplasty (-5.07/10 points, P<0.01) and vertebroplasty (-4.55/10, P<0.01) was superior to that for non-surgical management (-2.17/10), while no difference was found between balloon kyphoplasty/vertebroplasty (P=0.35). Subsequent fractures occurred more frequently in the non-surgical management group (22 %) compared with vertebroplasty (11 %, P=0.04) and balloon kyphoplasty (11 %, P=0.01). Balloon kyphoplasty resulted in greater kyphosis reduction than vertebroplasty (4.8 masculine vs 1.7 degrees , P<0.01). Quality of life improvement showed superiority of balloon kyphoplasty over vertebroplasty (P=0.04), along with a trend for disability improvement (P=0.08). Cement extravasation was less frequent in the balloon kyphoplasty (P=0.01). Surgical intervention within the first 7 weeks yielded greater pain reduction than vertebral compression fractures treated later.	4

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
27. Sahgal A, Ma L, Weinberg V, et al. Reirradiation human spinal cord tolerance for stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys* 2012; 82(1):107-116.	4	19: 5 radiation myelopathy patients and 14 no-radiation myelopathy patients	To review the treatment for patients with spine metastases who initially received conventional EBRT and were reirradiated with 1-5 fractions of SBRT who did or did not subsequently develop radiation myelopathy.	SBRT given at least 5 months after conventional palliative RT with a reirradiation thecal sac P(max) nBED of 20-25 Gy(2/2) appears to be safe provided the total P(max) nBED does not exceed approximately 70 Gy(2/2), and the SBRT thecal sac P(max) nBED comprises no more than approximately 50% of the total nBED.	4
28. Lo SS, Teh BS, Mayr NA, et al. Stereotactic body radiation therapy for oligometastases. *Discov Med* 2010; 10(52):247-254.	7	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.	3
29. Pagani O, Senkus E, Wood W, et al. International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? *J Natl Cancer Inst* 2010; 102(7):456-463.	15	N/A	To present and discuss the available data supporting the local (surgery and RT) and chemotherapy options, possibly associated with cure in patients with metastatic breast cancer.	Large retrospective series show an association between surgical removal of the primary tumor or of lung metastases and improved long-term outcome in patients with oligometastatic disease. In the absence of data from prospective randomized studies, removal of the primary tumor or isolated metastatic lesions may be an attractive therapeutic strategy in this subset of patients, offering rapid disease control and potential for survival benefit. Some improvement in outcome may also be achieved with optimization of systemic therapies, possibly in combination with optimal local treatment.	4

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
30. 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.	7 (meta-analysis)	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.	2
31. 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.	15	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.	3

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
32. 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.	1	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

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
33. 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.	1	1,157 patients; 579 patients received single fractions of 8 Gy; 578 six 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

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
34. DiBiase SJ, Valicenti RK, Schultz D, Xie Y, Gomella LG, Corn BW. Palliative irradiation for focally symptomatic metastatic renal cell carcinoma: support for dose escalation based on a biological model. *J Urol* 1997; 158(3 Pt 1):746-749.	3c	107 patients with renal cell metastases at 150 sites	To determine the ability of RT to palliate focally symptomatic metastatic renal cell carcinoma and to assess whether the delivery of higher biologically effective dose was more likely to bring about a palliative response.	For the entire group 86% of patients derived a palliative response after treatment with irradiation, while 49% derived a complete palliative response. The median duration of palliation was 6 months (range 1 to 150). With respect to overall (that is, complete and partial) response rates, those presenting with high Karnofsky PS were most likely to respond (status ≥70 vs <70, 88% vs 78%, P<0.04). With respect to the rate of complete palliative response, PS (s status ≥70 vs <70, 55% vs 31%, P<0.03) and the use of higher biologically effective doses of irradiation (10-50 or greater Gy vs <50 Gy, 59% vs 39%, P=0.001) were associated with a statistically significant increased rate of response. The independent prognostic value of PS and higher biologically effective doses of irradiation were maintained in multivariate analysis. Despite the prevailing concept that renal cell carcinoma is generally resistant to RT, the overwhelming majority of patients in whom metastatic renal cell carcinoma developed were palliated with RT. A complete palliative response is more likely when higher biologically effective doses of irradiation are delivered, especially to patients with a relatively high PS.	2

Spinal Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
35. Onufrey V, Mohiuddin M. Radiation therapy in the treatment of metastatic renal cell carcinoma. *Int J Radiat Oncol Biol Phys* 1985; 11(11):2007-2009.	4	125 patients	Authors reviewed their experience in the treatment of metastatic renal cell carcinoma to determine the effectiveness of radiation in its palliation.	Most patients were referred for relief of bone pain (86), brain metastasis (12), spinal cord compression (9), and soft tissue masses (18). Total doses varied from 2000 rad to a maximum of 6000 rad. Response to treatment was evaluated on the basis of relief of symptoms, either complete, partial or no change. Results indicate a significantly higher response rate of 65% for total doses equal to or greater than a TDF of 70, as compared to 25% for doses lower than a TDF of 70. No difference in response was observed either for bone or soft tissue metastasis or visceral disease. Authors believe that metastatic lesions from adenocarcinomas of the kidney should be treated to higher doses to obtain maximum response rates.	4
36. Nguyen QN, Shiu AS, Rhines LD, et al. Management of spinal metastases from renal cell carcinoma using stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys* 2010; 76(4):1185-1192.	4	48 patients with 55 spinal metastases	To evaluate the outcomes associated with SBRT in the management of spinal metastases from renal cell carcinoma.	The actuarial 1-year spine tumor progression free survival was 82.1%. At pretreatment baseline, 23% patients were pain free; at 1 month and 12 months post-SBRT, 44% and 52% patients were pain free, respectively. No Grade 3-4 neurologic toxicity was observed. The data support SBRT as a safe and effective treatment modality that can be used to achieve good tumor control and palliation of pain associated with renal cell carcinoma spinal metastases. Further evaluation with randomized trials comparing SBRT to conventional RT may be warranted.	3
37. Sahgal A, Ma L, Gibbs I, et al. Spinal cord tolerance for stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys* 2010; 77(2):548-553.	9	24 total: 5 with radiation-induced myelopathy compared to 19 with no-radiation-induced myelopathy post SBRT	Dosimetric data are reported for five cases of radiation-induced myelopathy after SBRT to spinal tumors. Analysis per the BED model was performed.	The maximum point dose should be respected for spine SBRT. For single-fraction SBRT 10 Gy to a maximum point is safe, and up to 5 fractions an nBED of 30 to 35 Gy 2/2 to the thecal sac also poses a low risk of radiation myelopathy.	3

Evidence Table Key

Study Type Key

Numbers 1-7 are for studies of therapies while numbers 8-15 are used to describe studies of diagnostics.

1. Randomized Controlled Trial — Treatment
2. Controlled Trial
3. Observation Study
    a. Cohort
    b. Cross-sectional
    c. Case-control
4. Clinical Series
5. Case reviews
6. Anecdotes
7. Reviews
8. Randomized Controlled Trial — Diagnostic
9. Comparative Assessment
10. Clinical Assessment
11. Quantitative Review
12. Qualitative Review
13. Descriptive Study
14. Case Report
15. Other (Described in text)

Strength of Evidence Key

- Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.
- Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.
- Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.
- Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Abbreviations Key

CI = Confidence interval

CR = Complete response

CT = Computed tomography

EBRT = External-beam radiation therapy

nBED = Normal biologic effective dose

PET = Positron emission tomography

PR = Partial response

PS = Performance status

RR = Relative risk

RT = Radiation therapy

SBRT = Stereotactic body radiotherapy