Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. Lubitz JD, Riley GF. Trends in Medicare payments in the last year of life. *N Engl J Med* 1993; 328(15):1092-1096.	15	All Medicare beneficiaries in their last year of life	Study examines trends in the proportion of Medicare expenditures for persons 65 years of age or older in their last year of life to determine whether there were any changes from 1976 to 1988.	Medicare costs for decedents rose from $3,488 per person/year in 1976 to $13,316 in 1988. However, Medicare payments for decedents as a percentage of the total Medicare budget changed little, fluctuating between 27.2% and 30.6% during the study period. Payments for care during the last 60 days of life expressed as a percentage of payments for the last year also held steady at about 52%.	1
2. American Cancer Society. Cancer facts and figures 2005. Atlanta, GA. *American Cancer Society* 2006:20.	15	N/A	Annual report on the state of cancer in the US.	Presents cancer incidence rates for most prevalent forms of the disease.	2
3. Dale RG, Jones B. Radiobiologically based assessments of the net costs of fractionated radiotherapy. *Int J Radiat Oncol Biol Phys* 1996; 36(3):739-746.	15 (Essay)	N/A	To describe the limitations of RCTs and how modeling can improve those trials.	Authors argue for modeling studies as a way to design better trials and as a supplement to information from trials.	4
4. Janjan NA. Radiotherapeutic approaches to cancer pain management. *Highlights in Oncol Prac* 1997; 14:103-113	N/A	N/A	Book chapter.	N/A	N/A
5. Plunkett TA, Smith P, Rubens RD. Risk of complications from bone metastases in breast cancer. implications for management. *Eur J Cancer* 2000; 36(4):476-482	15	859 patients who developed bone metastasis	Retrospective analysis on description of patterns of occurrence and outcomes for 4 groups of patients: 1) bone disease only; 2) bone and soft tissue disease; 3) bone and pleuro-pulmonary disease; and 4) bone and liver disease.	The time to long bone fracture was similar for all groups, but the least number of such fractures occurred in Group 4. Patients in Group 1 were most likely to require radiotherapy to painful osseous deposits and most rapidly developed spinal cord compression. The results suggest that patients with disease confined to the skeleton at the diagnosis of bone metastases are most likely to develop skeletal-related complications from advanced breast cancer. Such patients may benefit most from treatment with bisphosphonates.	2
6. Sherry MM, Greco FA, Johnson DH, Hainsworth JD. Breast cancer with skeletal metastases at initial diagnosis. Distinctive clinical characteristics and favorable prognosis. *Cancer* 1986; 58(1):178-182.	15	15	Examined outcomes for bone cancer patients retrospectively identified as having bone metastasis.	Since patients with stage IV breast cancer and metastases limited to the skeleton often have prolonged survival, complications from bone metastases (eg, pathologic fracture, epidural spinal cord compression) and other intercurrent illnesses should be managed aggressively.	3

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7. Sherry MM, Greco FA, Johnson DH, Hainsworth JD. Metastatic breast cancer confined to the skeletal system. An indolent disease. *Am J Med* 1986; 81(3):381-386.	15	86 patients with disease confined to skeleton	Study of outcomes comparing bone cancer patients retrospectively identified as having metastatic disease confined to skeleton with bone cancer patients with other presentations of metastases.	The median survival for this group of patients was 48 months, compared with a median survival of 17 months in patients with breast cancer metastatic to other sites. Metastatic breast cancer confined to the skeletal system is a common entity that can be defined clinically, is highly responsive to treatment, and is frequently associated with prolonged survival.	3
8. Knudson G, Grinis G, Lopez-Majano V, et al. Bone scan as a stratification variable in advanced prostate cancer. *Cancer* 1991; 68(2):316-320.	15 (Retrospective analysis)	76	The serial TC-99m bone scans of patients with stage D-2 prostate cancers were reviewed.	Sites of metastases in skeletal areas in decreasing order were vertebrae, ribs, pelvis, long bones, and skull. Patients with one or two involved skeletal areas had significantly better outcomes. Suggests that bone scans might be used as stratification variable in future prospective studies of stage D-2 prostate cancer.	3
9. Lai PP, Perez CA, Lockett MA. Prognostic significance of pelvic recurrence and distant metastasis in prostate carcinoma following definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 1992; 24(3):423-430.	15 (Retrospective analysis)	317 patients with recurrent prostate cancer among an initial set of 738	To determine the prognostic value of various factors among prostate cancer patients who recur to the pelvis or who subsequently present with distant metastases.	The prognostic factors that affect subsequent patient survival after pelvic recurrence include initial stage, disease-free interval from initial treatment, and salvage therapy with hormones. Patients with distant metastasis with or without pelvic recurrence showed statistically worse survival and were apparently not influenced by initial tumor stage, or disease-free interval from initial treatment.	3
10. Yamashita K, Denno K, Ueda T, et al. Prognostic significance of bone metastases in patients with metastatic prostate cancer. *Cancer* 1993; 71(4):1297-1302.	15 (Retrospective analysis)	76	To assess the prognosis among 3 groups of prostate cancer patients: I) those having bone metastases exclusively within the pelvis and the lumbar spine; II) having bone metastases exclusively outside these bones; and III) having bone metastases in both areas.	Among patients who responded to androgen deprivation (number not identified): group I survived significantly longer than did those in groups II or III. Because EOD and the distribution of histologic differentiation in groups I and II were similar, the results indicate that the presence of bone metastases outside the pelvis and the lumbar spine is predictive of short survival time. This prediction was not possible when EOD grading system was used.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
11. Sabbatini P, Larson SM, Kremer A, et al. Prognostic significance of extent of disease in bone in patients with androgen-independent prostate cancer. *J Clin Oncol* 1999; 17(3):948-957.	15 (Retrospective statistical analysis)	191	To evaluate the prognostic significance of a bone scan index (BSI) based on the weighted proportion of tumor involvement in individual bones, in relation to other factors and to survival in patients with androgen-independent prostate cancer.	In multiple-variable proportional hazards analyses, only BSI, age, hemoglobin, lactate dehydrogenase, and treatment arm were associated with survival. Further study is needed to assess the utility of serial BSI determinations in monitoring treatment effects but the measure may be particularly useful in the evaluation of agents for which PSA changes do not reflect clinical outcomes accurately.	3
12. Chang VT, Thaler HT, Polyak TA, Kornblith AB, Lepore JM, Portenoy RK. Quality of life and survival: the role of multidimensional symptom assessment. *Cancer* 1998; 83(1):173-179.	3a	218	The relation between survival and quality of life (QOL) measurements was tested among patients with malignancies at one of four sites (colon, breast, ovary, or prostate) who participated in a cross-sectional validation study of the Memorial Symptom Assessment Scale (MSAS), a measure of the frequency of, severity of, and distress caused by physical symptoms.	The MSAS physical symptom subscale score significantly predicts survival and adds to the prognostic information provided by KPS and extent of disease. Patients may be under-assessed regarding both the number and the severity of symptoms. Measurements of physical symptoms and related distress offer additional prognostic information concerning the survival of patients with cancer and may account for the predictive value of QOL scores.	3
13. Fielding LP, Henson DE. Multiple prognostic factors and outcome analysis in patients with cancer. Communication from the American Joint Committee on Cancer. *Cancer* 1993; 71(7):2426-2429.	15	N/A	Describes the establishment of a new Committee of the American Joint Committee on Cancer that has two objectives as follows: 1) to review the methods available to estimate outcome and, 2) to study certain tumors to determine whether an expanded list of prognostic factors can be formulated into new prognostic systems that will have scientific value and clinical utility for treatment selection and staging.	N/A	N/A
14. Grabowski CM, Unger JA, Potish RA. Factors predictive of completion of treatment and survival after palliative radiation therapy. *Radiology* 1992; 184(2):329-332.	4	96	To define prognostic factors that may reliably help determine survival and probability of completing a course of palliative radiation therapy.	KPS was consistently significant for probability of survival. At 8 months and 16 months, site of primary disease was significant, and at 16 months, solitary site of metastasis was also significant. Authors conclude that conventional factors, especially KPS, are useful in predicting the likelihood of completing radiation therapy and of subsequent survival for patients undergoing palliative treatment.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
15. Portenoy RK, Miransky J, Thaler HT, et al. Pain in ambulatory patients with lung or colon cancer. Prevalence, characteristics, and effect. *Cancer* 1992; 70(6):1616-1624.	3a	145 lung 181 colon	Prospective phone interview with lung and colon cancer patients to evaluate the epidemiology and effect of pain in ambulatory patients with cancer who are undergoing active therapy.	Pain is prevalent among well-functioning ambulatory patients and substantially compromises function in approximately half of the patients who experience it. Pain is a complex symptom; aspects other than intensity, such as frequency, strongly influence its effect.	3
16. Reuben DB, Mor V, Hiris J. Clinical symptoms and length of survival in patients with terminal cancer. *Arch Intern Med* 1988; 148(7):1586-1591.	4	N/A	To examine the correlation of 14 easily assessable clinical symptoms with survival in patients with terminal cancer.	Performance status was the most important clinical factor in estimating survival time, but five other symptoms had independent predictive value as well (shortness of breath, problems eating or anorexia, trouble swallowing, dry mouth, and weight loss). Findings illustrate the value of biologically "soft" clinical data in predicting survival in terminal cancer.	3
17. Borre M, Nerstrom B, Overgaard J. The natural history of prostate carcinoma based on a Danish population treated with no intent to cure. *Cancer* 1997; 80(5):917-928.	3	719	To describe the natural history of prostate carcinoma when it goes untreated in a national population.	Disease specific survival rates at 1, 5, and 10 years were 80%, 38%, and 17%, respectively, and 62% of the patients died primarily of prostate carcinoma. A multivariate analysis demonstrated a statistically significant relationship between disease specific death and T classification, tumor differentiation, and erythrocyte sedimentation rate at diagnosis.	2
18. Greenwald HP, Bonica JJ, Bergner M. The prevalence of pain in four cancers. *Cancer* 1987; 60(10):2563-2569.	3	N/A	To describe the problem of pain among cancer patients for early as well as late stages of the disease and for those receiving care in the community as well as specialized treatment centers.	Serious pain may occur in all cancer stages, and often represents an ongoing medical problem. The data suggest that many patients may benefit from earlier and more aggressive use of available anti-pain treatment methods.	3
19. Perez CA, Cosmatos D, Garcia DM, Eisbruch A, Poulter CA. Irradiation in relapsing carcinoma of the prostate. *Cancer* 1993; 71(3 Suppl):1110-1122.	3	N/A	To describe outcomes for patients irradiated upon recurrence of prostate carcinoma.	Various outcomes presented for seemingly different subpopulations of patients.	3
20. Brown JE, Cook RJ, Major P, et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. *J Natl Cancer Inst* 2005; 97(1):59-69.	3	441	Retrospective analysis of patients who were in control arms of various Phase II trials (of zoledronic acid) to determine whether bone markers have prognostic value in prostate and NSCLC patients with bone metastases.	Baseline and recent bone marker levels were predictive of negative clinical outcomes in patients with bone metastases secondary to prostate cancer and to NSCLC N-telopeptide levels were more consistent prognostic indicators than bone-specific alkaline phosphatase for all tumor types, reflecting the key role of osteolysis in the development of skeletal complications.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
21. Brown JE, Thomson CS, Ellis SP, Gutcher SA, Purohit OP, Coleman RE. Bone resorption predicts for skeletal complications in metastatic bone disease. *Br J Cancer* 2003; 89(11):2031-2037.	3	121	To assess the relationships between the rate of bone resorption (measured by urinary N-telopeptide (Ntx) excretion) and a range of skeletal complications.	There is a strong correlation between the rate of bone resorption and the frequency of skeletal complications in metastatic bone disease. N-telopeptide appears useful in the prediction of patients most likely to experience skeletal complications and thus benefit from bisphosphonate treatment.	2
22. Emanuel EJ, Fairclough DL, Slutsman J, Emanuel LL. Understanding economic and other burdens of terminal illness: the experience of patients and their caregivers. *Ann Intern Med* 2000; 132(6):451-459.	15	988 patients, 893 caregivers in 6 urban areas	Interviews were conducted with terminally ill patients and their caregivers to determine the mechanism for economic and noneconomic burdens of terminal illness and to identify potential ameliorating interventions.	Substantial care needs are an important cause of the economic and other burdens imposed by terminal illness. Through empathy, physicians may be able to ameliorate some of these burdens.	3
23. Stafford RS, Cyr PL. The impact of cancer on the physical function of the elderly and their utilization of health care. *Cancer* 1997; 80(10):1973-1980.	3	9,745	Analyzed national sample of Medicare beneficiaries to evaluate the effects of cancer on a range of QOL and health care utilization measures within an elderly population.	Cancer was reported by 17% of the elderly. These individuals were sicker and had worse QOL than non-cancer patients but were generally satisfied with their care.	2
24. Cohen HJ. Cancer and the functional status of the elderly. *Cancer* 1997; 80(10):1883-1886.	15 (Editorial)	N/A	To opine on cancer care for the elderly.	It would be beneficial to include a geriatrician in the management of elderly cancer patients.	4
25. Morita T, Tsunoda J, Inoue S, Chihara S. Contributing factors to physical symptoms in terminally-ill cancer patients. *J Pain Symptom Manage* 1999; 18(5):338-346.	3	350 total	A prospective study of 2 groups of hospice patients to identify the factors contributing to physical symptoms.	Frequency of various symptoms described. In addition, study found that opioid requirement was positively correlated with the presence of bone metastasis, and negatively correlated with age and brain involvement. Additional opioids were frequently used in the final 48 hours in cases with lung/pleura neoplasms.	3
26. Vigano A, Bruera E, Jhangri GS, Newman SC, Fields AL, Suarez-Almazor ME. Clinical survival predictors in patients with advanced cancer. *Arch Intern Med* 2000; 160(6):861-868.	3	227	Patients with terminal cancer were followed prospectively to establish the survival after diagnosis of terminal disease and to determine the predictors of survival.	92% mortality within 30 month observation window. Simple clinical and laboratory assessments were useful predictors of survival.	3
27. Janjan NA. Radiation for bone metastases: conventional techniques and the role of systemic radiopharmaceuticals. *Cancer* 1997; 80(8 Suppl):1628-1645.	7	N/A	Describes management of patients with bone metastasis.	Efficient and comprehensive management of bone metastases is imperative because of the associated symptoms, prior therapies, complex underlying medical problems, and clinical presentations that often require emergent interventions.	4

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28. Joranson DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. *JAMA* 2000; 283(13):1710-1714.	3	National sample	Retrospective review of hospital ED admissions matched with records in two drug control national databases to evaluate the proportion of drug abuse related to opioid analgesics and the trends in medical use and abuse of 5 opioid analgesics used to treat severe pain: fentanyl, hydromorphone, meperidine, morphine, and oxycodone.	The trend of increasing medical use of opioid analgesics to treat pain does not appear to contribute to increases in the health consequences of opioid analgesic abuse.	2
29. Liu L, Meers K, Capurso A, Engebretson TO, Glicksman AS. The impact of radiation therapy on quality of life in patients with cancer. *Cancer Pract* 1998; 6(4):237-242.	3	24	RAND 36-item survey was used to evaluate the physical and mental status change during and after a course of radiation treatment in patients with cancer.	Patients who had higher mental component scores before treatment appeared to have higher, and improving, physical component scores throughout the course of evaluation. Along with complementary social support, the implementation of psychosocial support early and throughout the course of treatment may result in physical benefits and improving overall QOL.	3
30. Ward SE, Berry PE, Misiewicz H. Concerns about analgesics among patients and family caregivers in a hospice setting. *Res Nurs Health* 1996; 19(3):205-211.	3	35	Concerns of hospice patients and family caregivers were compared (using a questionnaire) to determine whether they were similar in terms of need for pain management.	There was no correlation between caregiver and patient concerns and means for the two groups were similar, indicating that within a given dyad either the patient or the caregiver may have greater concerns.	3
31. Weissman DE. Doctors, opioids, and the law: the effect of controlled substances regulations on cancer pain management. *Semin Oncol* 1993; 20(2 Suppl 1):53-58.	7	N/A	Paper reviews the historical basis and current structure of the system that regulates opioid use.	Four potential ways in which controlled substances regulations and policies can affect medical care are discussed and physicians are urged to work with state regulatory agencies to identify regulatory impediments to appropriate patient care.	2
32. Janjan NA, Payne R, Gillis T, et al. Presenting symptoms in patients referred to a multidisciplinary clinic for bone metastases. *J Pain Symptom Manage* 1998; 16(3):171-178.	3	108	Wisconsin Brief Pain Inventory was given to patients with bone metastasis in order to describe their presenting symptoms.	Pain was rated moderate to severe (levels 4-10) in 79% and severe in 23% of patients. Only 45% of patients experienced good relief from the prescribed analgesics, and 23% of patients indicated that the prescribed analgesics were ineffective. This demonstrates that bone metastases incur significant pain that is often undertreated with analgesics before antineoplastic therapy is administered.	3
33. Riley GF, Lubitz JD. Longitudinal patterns of Medicare use by cause of death. *Health Care Financ Rev* 1989; 11(2):1-12.	3	National sample	Medicare claims data were used to study the use of health services before death for different causes.	Persons dying of nephritis, chronic obstructive pulmonary disease, and diabetes mellitus incurred consistently high expenses for 6 years before death. Costs for cancer decedents were also high, especially in the last 2 years of life.	2

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34. Riley GF, Potosky AL, Lubitz JD, Kessler LG. Medicare payments from diagnosis to death for elderly cancer patients by stage at diagnosis. *Med Care* 1995; 33(8):828-841.	3	National sample	SEER data linked to Medicare claims were used to examine health resource utilization for cancer patients from diagnosis to death.	Average payments by phase varied among cancer sites, especially in the initial care phase, where payments were highest for lung and colorectal cancers ($17,500 in 1990 dollars) and lowest for female breast cancer ($8,913). Total Medicare payments from diagnosis to death were highest for persons with bladder cancer ($57,629) and lowest for those with lung cancer ($29,184). Low payments for persons with lung cancer corresponded to brief survival times.	2
35. Emanuel EJ, Young-Xu Y, Levinsky NG, Gazelle G, Saynina O, Ash AS. Chemotherapy use among Medicare beneficiaries at the end of life. *Ann Intern Med* 2003; 138(8):639-643.	3a	All cancer deaths in Mass. And 5% of those from cancer	Retrospective cohort analysis to determine the frequency and duration of chemotherapy use in the last 6 months of life stratified by type of cancer, age, and sex.	Among patients who died of cancer, chemotherapy was used frequently in the last 3 months of life. The cancer's responsiveness to chemotherapy does not seem to influence whether dying patients receive chemotherapy at the end-of-life.	2
36. Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC. Trends in the aggressiveness of cancer care near the end of life. *J Clin Oncol* 2004; 22(2):315-321.	3	28,777 patients who died within 1-year of diagnosis	To characterize the aggressiveness of end-of-life cancer treatment for older adults on Medicare, and its relationship to the availability of healthcare resources.	The treatment with chemotherapy of cancer patients near death is becoming increasingly aggressive over time.	2
37. Earle CC, Neville BA, Landrum MB, et al. Evaluating claims-based indicators of the intensity of end-of-life cancer care. *Int J Qual Health Care* 2005; 17(6):505-509.	15	Large sample (>48K patients) used to validate measures	To evaluate measures that could use existing administrative data to assess the intensity of end-of-life cancer care.	The usefulness of these measures will depend on whether the concept of intensity of care near death can be further validated as an acceptable and important quality issue.	3
38. Porzsolt F. Goals of palliative cancer therapy: scope of the problem. *Cancer Treat Rev* 1993; 19 Suppl A:3-14.	7	N/A	Describes some of the problems of palliative cancer therapy and proposes possible solutions.	Concept of Tumor vs Host Disease (TvHD) is discussed, and different end points for palliation are defined for daily oncology practice and oncology research. Finally, a way to collect data outside randomized trials is proposed, and the need for data collection is emphasized.	4

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39. Baicker K, Chandra A. Medicare spending, the physician workforce, and beneficiaries' quality of care. *Health Aff (Millwood)* 2004; Suppl Web Exclusives:W184-197.	15	N/A	To examine the relationship between spending, workforce and quality.	We find that states with higher Medicare spending have lower-quality care. One mechanism for this trade-off may be the mix of the provider workforce: States with more general practitioners use more effective care and have lower spending, while those with more specialists have higher costs and lower quality.	4
40. Hillner BE, Weeks JC, Desch CE, Smith TJ. Pamidronate in prevention of bone complications in metastatic breast cancer: a cost-effectiveness analysis. *J Clin Oncol* 2000; 18(1):72-79.	15	Patients from 2 trials (numbers not presented)	Retrospective evaluation of the cost-effectiveness of pamidronate using the results of two randomized trials that evaluated pamidronate 90 mg administered intravenously every month vs placebo.	The cost of pamidronate therapy exceeded the cost savings from prevented adverse events.	3
41. Dranitsaris G, Hsu T. Cost utility analysis of prophylactic pamidronate for the prevention of skeletal related events in patients with advanced breast cancer. *Support Care Cancer* 1999; 7(4):271-279.	15	25	A retrospective cost-utility analysis was performed from a Canadian health care system perspective to estimate the incremental cost-effectiveness of pamidronate in patients with advanced breast cancer.	Results of the decision model revealed an incremental pamidronate cost of $18,700 per quality-adjusted life year gained. The results of the sensitivity analysis suggested that this estimate was dependent on the cost of treating skeletal related events, particularly bone surgery. Even though pamidronate has a high drug acquisition cost, the results of the cost-utility analysis suggest that this agent does provide patients with a substantial quality-adjusted survival benefit at a reasonable cost to the Canadian health care system.	3
42. Gainford MC, Dranitsaris G, Clemons M. Recent developments in bisphosphonates for patients with metastatic breast cancer. *BMJ* 2005; 330(7494):769-773.	7	N/A	Literature review to report on developments in the use of bisphosphonates for treating metastatic breast cancer.	Bisphosphonates are an established therapy for patients with bone metastasis. Randomized Controlled Trials (RCTs) confirm benefit. Benefit is time dependent, occurring >6 months. Patients with only bone disease benefit most. Previous RCTs were highly selective in recruiting patients so benefits of bisphosphonates in poor prognosis patients remain unclear.	3
43. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. *J Clin Oncol* 1998; 16(6):2038-2044.	1	382	RCT to determine the long-term effectiveness and safety of continued treatment with intravenous pamidronate infusions for up to 2 years.	The risk for osteolytic bone lesion complications in metastatic breast cancer was significantly decreased with monthly infusions of 90 mg of pamidronate, and this effect was maintained for at least 2 years.	1

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44. Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med* 1996; 335(24):1785-1791.	1	382	Short-term version of study #43, above.	Monthly infusions of pamidronate as a supplement to chemotherapy can protect against skeletal complications in women with stage IV breast cancer who have osteolytic bone metastases.	1
45. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000; 88(5):1082-1090.	1	754	To present follow-up results regarding the effects of long term (up to 24 months) pamidronate treatment in women with breast carcinoma and osteolytic metastases.	Monthly infusions of 90 mg of pamidronate as a supplement to antineoplastic therapy were found to be well tolerated and superior to antineoplastic therapy alone in preventing skeletal complications and palliating symptoms for at least 24 months in breast carcinoma patients with osteolytic bone metastases.	1
46. 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	898	To determine whether 8 Gy delivered in a single treatment fraction provides pain and narcotic relief that is equivalent to that of the standard treatment course of 30 Gy delivered in 10 treatment fractions over 2 weeks.	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 retreatment but had less acute toxicity than the 30 Gy arm.	1
47. Centers for Medicare and Medicaid Services, Office of the Actuary. http://www.cms.hhs.gov/NationalHealthExpendData/.	N/A	N/A	Government publication.	N/A	N/A
48. Kaiser Family Foundation / Harvard School of Public Health. Health Care Costs Survey. *USA Today*, August, 2005.	13	National Survey	Newspaper account of Kaiser report on costs of US healthcare.	Costs are high and going up.	2
49. Appleby J. More insured workers unable to pay medical bills. *USA Today*, April, 2005.	15	N/A	Newspaper article.	Lack of insurance still a problem in US.	4
50. Arozullah AM, Calhoun EA, Wolf M, et al. The financial burden of cancer: estimates from a study of insured women with breast cancer. *J Support Oncol* 2004; 2(3):271-278.	3	156	Interviews of patients to provide estimates of the costs incurred by a cohort of breast cancer patients who were covered by private, Medicare, or Medicaid health insurance.	Even among women with comprehensive health insurance policies, the out of pocket financial burden of breast cancer can be substantial.	3
51. Emanuel EJ. Cost savings at the end of life. What do the data show? *JAMA* 1996; 275(24):1907-1914.	7	N/A	To review the research on end-of-life resource utilization.	Although there is not definitive evidence that hospice and advance directives (ADs) save money, both should be encouraged because they certainly do not cost more and they provide a means for patients to exercise their autonomy over end-of-life decisions.	3

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52. Emanuel EJ, Ash A, Yu W, et al. Managed care, hospice use, site of death, and medical expenditures in the last year of life. *Arch Intern Med* 2002; 162(15):1722-1728.	3	37,933 in MA and 27,685 in CA.	Medicare claims data used to evaluate the effect of managed care on the use of hospice and site of death and to determine how hospice affects the expenditures for the last year of life.	Medicare-insured decedents in California were more than 4 times more likely to be enrolled in managed care organizations (MCOs), were 50% more likely to use a hospice, and had a 30% lower hospitalization rate than decedents in Massachusetts, yet there are few differences in out-of-hospital deaths or expenditures in the last year of life. However, patients with cancer using hospice did have significant savings.	2
53. Gabel J, Claxton G, Gil I, et al. Health benefits in 2005: premium increases slow down, coverage continues to erode. *Health Aff (Millwood)* 2005; 24(5):1273-1280.	3	N/A	Description of job-based health insurance in spring 2005 and how it has changed during recent years.	Premiums rose 9.2%, the first year of single-digit increases since 2000. The percentage of firms offering health benefits has fallen from 69%in 2000 to 60% in 2005.	2
54. Haupt BJ. Characteristics of hospice care discharges and their length of service: United States, 2000. *Vital Health Stat 13* 2003; (154):1-36.	3	621,100 discharges	Presents data on hospice care discharges for 2000. Selected trend data are also presented.	Cancer is the most common primary admission diagnosis, but the proportion decreased from 75% in 1992 to 58% in 2000. Most of the discharges did not receive timely care. 63% of discharges received hospice care for less than 30 days. The average length of service was 46.9 days, and the median length of service was 15.6 days.	2
55. Mertens WC, Hoople NE, Rodrigues C, Lindenauer PK, Benjamin EM. Association of admission date with cancer patient survival at a regional hospice: utility of a statistical process control analysis. *Am J Hosp Palliat Care* 2004; 21(4):275-284.	3	2,126	To assess mean length-of-stay (LOS) over time and to determine the factors, including date of death, which are independently associated with LOS.	Mean LOS is associated with date of admission to hospice independent of other associated factors. LOS decreases do not occur in a gradual, continuous fashion but suddenly and intermittently, and they are not associated with changes in referral numbers or readmissions.	3
56. Slutsman J, Emanuel LL, Fairclough D, Bottorff D, Emanuel EJ. Managing end-of-life care: comparing the experiences of terminally Ill patients in managed care and fee for service. *J Am Geriatr Soc* 2002; 50(12):2077-2083.	3	988 patients, 893 caregivers	Interviews of patients and caregivers conducted in an effort to compare outcomes between populations of terminally ill patients enrolled in MCO and fee for service (FFS) healthcare delivery systems.	Overall, the two populations of terminally ill patients were found to have comparable outcomes but MCO patients were more likely than their FFS counterparts to use an inconvenient hospital, spend more than 10% of their income on medical care, and have been bedridden more than 50% of the time during the last 4 weeks of life.	3
57. Smith C, Cowan C, Sensenig A, Catlin A. Health spending growth slows in 2003. *Health Aff (Millwood)* 2005; 24(1):185-194.	3	N/A	Description of healthcare spending.	The pace of health spending growth slowed in 2003 for the first time in seven years, driven in part by a slowdown in public spending growth. U.S. health care spending rose 7.7% in 2003, much slower than the 9.3% growth in 2002.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
58. National Health Care Expenditures 1960-2005. Centers for Medicare and Medicaid Services, Office of the Actuary: Data from the National health Statistics Group. http://www.cms.hhs.gov/NationalHealthExpendData/02_NationalHealthAccountsHistorical.asp#TopOfPage.	N/A	N/A	Government statistics.	N/A	N/A
59. A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). The SUPPORT Principal Investigators. *JAMA* 1995; 274(20):1591-1598.	3 and then 1	4,301 and 4,804	A 2-year prospective observational study followed by a 2-year controlled clinical trial to improve end-of-life decision making and reduce the frequency of a mechanically supported, painful, and prolonged process of dying.	The phase I observation of SUPPORT confirmed substantial shortcomings in care for seriously ill hospitalized adults. The phase II intervention failed to improve care or patient outcomes. Enhancing opportunities for more patient-physician communication, although advocated as the major method for improving patient outcomes, may be inadequate to change established practices. To improve the experience of seriously ill and dying patients, greater individual and societal commitment and more proactive and forceful measured may be needed.	2
60. *Approaching Death: Improving care at the end of life*. Washington D.C.: National Academy Press; 1997.	15	N/A	Report from IOM.	N/A	N/A
61. Covinsky KE, Fuller JD, Yaffe K, et al. Communication and decision-making in seriously ill patients: findings of the SUPPORT project. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. *J Am Geriatr Soc* 2000; 48(5 Suppl):S187-193.	2	Not reported in abstract	Large trial (see #58) to describe patient preferences in terminally seriously ill patients, and to evaluate how effectively patient preferences are communicated.	Physicians and surrogates are often unaware of seriously ill patients' preferences. The care provided to patients is often not consistent with their preferences and is often associated with factors other than preferences or prognoses. Improving these deficiencies in end-of-life care may require systematic change rather than simple interventions.	2
62. Gamble ER, McDonald PJ, Lichstein PR. Knowledge, attitudes, and behavior of elderly persons regarding living wills. *Arch Intern Med* 1991; 151(2):277-280.	3	75	Knowledge, attitudes, and behavior of elderly persons regarding living wills were explored in a rural county in eastern North Carolina. A questionnaire was administered to 75 ambulatory elderly persons by personal interview at community dining sites.	Although 52% were familiar with living wills and 81% said they wanted to discuss end-of-life issues with their physicians, this group of patients did not make use of living wills. Recommendations are made to improve the situation.	3

Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
63. Garas N, Pantilat SZ. Chapter 49. Advance Planning For End-of-Life Care. *AHRQ Evidence Reports, Numbers 1-60.* Washington, D.C.: Agency for Healthcare Research and Quality http://www.ahrq.gov/clinic/patientsafety/chap49.htm.	N/A	N/A	Describes Advance Planning for end-of-life options.	Presents templates for a "living will" (which is the simpler approach) and a "durable power of attorney for healthcare" which is a more comprehensive document.	N/A
64. Teno J, Lynn J, Wenger N, et al. Advance directives for seriously ill hospitalized patients: effectiveness with the patient self-determination act and the SUPPORT intervention. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. *J Am Geriatr Soc* 1997; 45(4):500-507.	3a then 1	9,105	Observational cohort study conducted for 2 years before and for 2 years after the Patient Self-determination Act (PSDA), with a randomized, controlled trial of an additional intervention to improve decision-making after PSDA (POST+SUPPORT) conducted to assess the effectiveness of written ADs in the care of seriously ill, hospitalized patients.	ADs did not substantially enhance physician-patient communication or decision-making about resuscitation. This lack of effect was not altered by the PSDA or by the enhanced efforts in SUPPORT, although these interventions each substantially increased documentation of existing ADs. Current practice patterns indicate that increasing the frequency of ADs is unlikely to be a substantial element in improving the care of seriously ill patients.	1
65. Teno JM, Licks S, Lynn J, et al. Do advance directives provide instructions that direct care? SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. *J Am Geriatr Soc* 1997; 45(4):508-512.	3	4,804	Follow-on study (to #63) to evaluate whether the lack of effect of ADs on decision-making in SUPPORT might arise, in part, from the content of the actual documents.	ADs placed in the medical records of seriously ill patients often did not guide medical decision-making beyond naming a healthcare proxy or documenting general preferences in a standard living will format. Even when specific instructions were present, care was potentially inconsistent in half of the cases.	2
66. Wenger NS, Phillips RS, Teno JM, et al. Physician understanding of patient resuscitation preferences: insights and clinical implications. *J Am Geriatr Soc* 2000; 48(5 Suppl):S44-51.	3	N/A	Another follow-on (to SUPPORT trial) to describe physician understanding of patient preferences concerning cardiopulmonary resuscitation (CPR) and to assess the relationship of physician understanding of patient preferences with DNR orders and in-hospital CPR.	Physicians often misunderstand seriously ill, hospitalized patients' resuscitation preferences, especially preferences to forego CPR. Factors associated with misunderstanding suggest that physicians infer patients' preferences without asking the patient.	3
67. Good care of the dying patient. Council on Scientific Affairs, American Medical Association. *JAMA* 1996; 275(6):474-478.	15	N/A	Guideline to establish future directions for establishing high quality care for terminal patients.	AMA should: 1. Encourage research into needs of dying patients; 2. Encourage educational programs for providers on caring for dying patients; 3. Support improved reimbursement for those providers who are important for caring for terminal patients.	4

Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
68. Christakis NA, Iwashyna TJ. Attitude and self-reported practice regarding prognostication in a national sample of internists. *Arch Intern Med* 1998; 158(21):2389-2395.	15	697 respondents (53%)	Mail survey of internists to discern physicians' attitudes and behavior with respect to hospice care.	Internists show significant support for, and utilization of, hospice and they endorse a length of stay that is longer than currently observed. These findings suggest that it may be possible to increase both the number of patients using hospice and their duration of use of hospice.	3
69. Emanuel LL, von Gunten CF, Ferris FD. *The Education for Physicians on End-of-Life Care (EPEC) Curriculum*; 1999.	15	N/A	Book.	N/A	N/A
70. Hanson LC, Tulsky JA, Danis M. Can clinical interventions change care at the end of life? *Ann Intern Med* 1997; 126(5):381-388.	15	N/A	Review of studies examining factors that might influence end-of-life care in order to determine if clinical interventions can have an effect.	To change care at the end-of-life, intensive educational interventions for physicians and broad institutional programs seem more promising than ADs.	3
71. Lamont EB, Christakis NA. Some elements of prognosis in terminal cancer. *Oncology (Williston Park)* 1999; 13(8):1165-1170; discussion 1172-1164, 1179-1180.	15 (Essay)	N/A	To consider two types of processes — foreseeing and foretelling — that play a role in the way physicians consider prognosis.	Physicians often make unwitting, large, and generally optimistic errors in foreseeing patients' prognoses. They also may make more conscious, but equally large, optimistic errors in foretelling prognoses to patients. The net effect is that patients may become twice removed from the truth about their illness, both times toward a falsely optimistic prognosis.	4
72. Lo B, McLeod GA, Saika G. Patient attitudes to discussing life-sustaining treatment. *Arch Intern Med* 1986; 146(8):1613-1615.	15	28 patients <65 69 patients >65 55 healthy patients	Administered survey to three groups of patients to determine attitudes towards discussing life-sustaining therapy.	Show that a substantial percentage (but not overwhelming majority) have given thought to life-sustaining therapy and recommend that physicians initiate conversation about this when appropriate.	3
73. Muldoon MF, Barger SD, Flory JD, Manuck SB. What are quality of life measurements measuring? *BMJ* 1998; 316(7130):542-545.	15 (Essay)	N/A	Presents framework for assessing QOL.	Divides QOL into measures of objective functioning and appraisals of well-being.	4
74. Zhong Z, Lynn J. Review of the Lamont/Christakis Article. *Oncology* 1999; 13:1172-1173.	15	N/A	Review of an article.	N/A	N/A

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
75. Blitzer PH. Reanalysis of the RTOG study of the palliation of symptomatic osseous metastasis. *Cancer* 1985; 55(7):1468-1472.	1	759	Reanalyze RTOG 74-02 using logistic regression multivariate analysis, grouping solitary and multiple metastasis groups and using stricter end-point of pain control.	For all endpoints (permanent complete pain relief, any CR, freedom from retreatment, or permanent CR and no narcotic need) 270X15 and 300X10 were more effective than 300X5, 400X5, and 500X5. Logistic regression suggested that only number of fractions was significant variable; dose/fraction, solitary vs multivariate metastasis, or interactive terms in model were not significant.	1
76. Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the Study by the Radiation Therapy Oncology Group. *Cancer* 1982; 50(5):893-899.	1	1,016	RTOG 74-02 determining effect of different fractionation patterns on pain control, narcotic need, and freedom from retreatment. Stratified for single vs multivariate metastasis.	• No significant difference in any fractionation but trend towards more complete relief with 270X15 and 400X5. • In multivariate metastasis group 300X10 not better than 300X5, 400X5, or 500X5.	1
77. Janjan NA. An emerging respect for palliative care in radiation oncology. *J Palliat Med* 1998; 1(1):83-88.	3b	N/A	Evaluation of education in palliative radiotherapy and palliative care in radiation oncology training programs.	Expand education in palliative radiotherapy.	3
78. SBU-The Swedish Council on Technology Assessment in Health Care. *Acta Oncologica* 1997; 35(Suppl 6; Vol 1):89-97.	15	N/A	One of two reports directed at policy makers aimed at improving the quality of care for the terminal patient and for providing palliative care	N/A	4
79. Steenland E, Leer JW, van Houwelingen H, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol* 1999; 52(2):101-109.	1	1,171	RCT to determine whether a single fraction of radiotherapy that is considered more convenient to the patient is as effective as a dose of multiple fractions for palliation of painful bone metastases.	The global analysis of the Dutch study indicates the equality of a single fraction as compared to a 6 fraction treatment in patients with painful bone metastases provided that 4 times more retreatments are accepted in the single dose group. This equality is also shown in long term survivors.	1
80. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. *Radiother Oncol* 1999; 52(2):111-121.	1	765	RCT to compare a single fraction of 8 Gy with a course of multifraction radiotherapy in terms of long-term benefits and short-term side effects in patients with painful skeletal metastases.	A single fraction of 8 Gy is as safe and effective as a multifraction regimen for the palliation of metastatic bone pain for at least 12 months. The greater convenience and lower cost make 8 Gy single fraction the treatment of choice for the majority of patients.	1
81. Barak F, Werner A, Walach N, Horn Y. The palliative efficacy of a single high dose of radiation in treatment of symptomatic osseous metastases. *Int J Radiat Oncol Biol Phys* 1987; 13(8):1233-1235.	2	N/A	To evaluate the efficacy of a high single dose of radiation on pain relief, with the goal of reducing the number of radiation sessions to a minimum.	Response to radiation therapy was 71.3% lasting up to 6 and 12 months in 37.3% and 20.9% of cases respectively.	3

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
82. Chow E, Lutz S, Beyene J. A single fraction for all, or an argument for fractionation tailored to fit the needs of each individual patient with bone metastases? *Int J Radiat Oncol Biol Phys* 2003; 55(3):565-567.	15	N/A	Editorial discussing the dose factorization controversy for localized radiation therapy of bone metastases.	Optimal therapy is likely to be dependent on patient factors more so than efficacy as numerous trials have demonstrated no real difference between the options.	N/A
83. Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clin Oncol (R Coll Radiol)* 1989; 1(2):59-62.	1	29	2400/6 fx/2-3 wks vs 800/1 fx. Spinal disease excluded; linear analog scale used.	All patients had good to excellent palliation but 25% of single fraction group required retreatment.	1
84. Hoskin PJ, Price P, Easton D, et al. A prospective randomised trial of 4 Gy or 8 Gy single doses in the treatment of metastatic bone pain. *Radiother Oncol* 1992; 23(2):74-78.	1	270	8 Gy vs 4 Gy single fraction.	Increased pain relief and decreased probability of retreatment with 8 Gy.	1
85. Jeremic B. Single fraction external beam radiation therapy in the treatment of localized metastatic bone pain. A review. *J Pain Symptom Manage* 2001; 22(6):1048-1058.	7	N/A	Review of what is known about fractionated treatment of localized bone metastases.	All RCTs that evaluated differences in the outcomes associated with various fractionated regimens vs single fraction regimens unequivocally showed that single fraction regimens (mostly 8 Gy) are at least equal with various fractionated regimens. The single fraction regimens have an additional advantage of being more convenient to both patients and hospitals. However, some questions remain.	3
86. Kal HB. Single fraction radiotherapy is as effective as multiple fractions for palliating painful bone metastases. *Cancer Treat Rev* 2003; 29(4):345-347.	15 (Meta-analysis)	3,620 patients pooled from 7 studies	To compare the efficacy of different dose fractionization of localized bone metastasis.	No difference in pain relief between single and multiple fractions.	1
87. Koswig S, Budach V. [Remineralization and pain relief in bone metastases after after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study]. *Strahlenther Onkol* 1999; 175(10):500-508.	1	107	RCT to examine pain relief and recalcification following radiotherapy for bone metastases. Patients were stratified to primary tumor sites and randomized in 2 different fractionation schedules: 1 x 8 Gy vs 10 x 3 Gy. Pain relief was registered using of pain score, analgesic usage and subjective perception of pain.	The basis of pain response and recalcification is different. In mere consideration of pain a short-course fractionation is recommendable. This fractionation schedule is effective, well tolerable and short. In consideration of recalcification a more fractionated schedule is recommendable because the biological efficacy is higher and this leads to better stabilization.	1

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
88. McQuay HJ, Collins SL, Carroll D, Moore RA. Radiotherapy for the palliation of painful bone metastases. *Cochrane Database Syst Rev* 2000; (2):CD001793.	15 (Meta-analysis)	20 studies	Assess pain relief from: 1) localized bone metastases achieved by radiotherapy, comparing the efficacy of different fractionation schedules, and 2) more generalized metastatic disease achieved by radiotherapy or radioisotopes.	Radiotherapy is clearly effective at reducing pain from painful bone metastases. There was no evidence of any difference in efficacy between different fractionation schedules, or indeed of a dose-response with total dose of radiation. For treatment of generalized bone pain both hemibody irradiation and radioisotopes can reduce the number of painful new sites.	1
89. Price P, Hoskin PJ, Easton D, Austin D, Palmer SG, Yarnold JR. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol* 1986; 6(4):247-255.	1	288	8 Gy/1 fx. vs 30 Gy/10 fx.	1. Onset of pain response equivalent. 2. Duration of response equivalent. 3. Incidence of CR greater with 8 Gy 22/49 (45%) vs 12/43 (28%). 4. Toxicity equivalent.	1
90. Sze WM, Shelley MD, Held I, Wilt TJ, Mason MD. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy--a systematic review of randomised trials. *Clin Oncol (R Coll Radiol)* 2003; 15(6):345-352.	15 (Meta-analysis)	12 studies	A systematic review of randomized studies, examining the effectiveness of single fraction radiotherapy vs multiple fraction radiotherapy for metastatic bone pain relief and prevention of bone complications, was conducted to help resolve the controversy about the efficacy of single dose vs fractionated RT.	Single fraction radiotherapy was as effective as multifraction radiotherapy in relieving metastatic bone pain. However, the re-treatment rate and pathological fracture rate were higher after single fraction radiotherapy. Studies with QOL and health economic end points are warranted to find out the optimal treatment option.	1
91. van den Hout WB, van der Linden YM, Steenland E, et al. Single- versus multiple-fraction radiotherapy in patients with painful bone metastases: cost-utility analysis based on a randomized trial. *J Natl Cancer Inst* 2003; 95(3):222-229.	15 (CEA of RCT)	1,157	A societal cost-utility analysis was performed on a Dutch RCT in which responses of patients with painful bone metastases were compared for those receiving a single-fraction treatment schedule of 8 Gy and those being treated with a schedule of six fractions of 4 Gy each.	Compared with multiple-fraction radiotherapy, single-fraction radiotherapy provides equal palliation and QOL and has lower medical and societal costs, at least in The Netherlands.	1
92. Wu JS, Wong R, Johnston M, Bezjak A, Whelan T. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys* 2003; 55(3):594-605.	15 (Meta-analysis)	16 RCT	Systematic review of extant RCT results was conducted to compare pain relief among various dose-fractionation schedules of localized RT in the treatment of painful bone metastases.	Meta-analysis of reported randomized trials shows no significant difference in complete and overall pain relief between single and multifraction palliative RT for bone metastases. No dose-response relationship could be detected by including data from the multifraction vs multifraction trials. Additional data are needed to evaluate the role of re-irradiation and the impact of RT on other treatment end points such as QOL.	1

Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
93. Alberts AS, Smit BJ, Louw WK, et al. Dose response relationship and multiple dose efficacy and toxicity of samarium-153-EDTMP in metastatic cancer to bone. *Radiother Oncol* 1997; 43(2):175-179.	4	24	Determine the optimal dose of samarium-153-EDTMP (153Sm-EDTMP) for effective palliation of painful metastases to bone.	153Sm-EDTMP provides adequate and safe palliation but multiple doses can only be given in 38% of patients. There is not a clear dose-response relationship. The length of pain control is satisfactory but not ideal and hospitalization for 4 days every 6-8 weeks is a disadvantage.	3
94. Anderson PM, Wiseman GA, Dispenzieri A, et al. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. *J Clin Oncol* 2002; 20(1):189-196.	2	30	A dose-escalation trial of 153Sm-EDTMP using peripheral-blood progenitor cells (PBPCs) or marrow support was conducted to treat metastatic bone cancer.	153Sm-EDTMP with PBPC support can provide bone-specific therapeutic irradiation (estimates of 39 to 241 Gy). Hematologic toxicity at 30 mCi 153Sm-EDTMP/kg requires PBPC grafts with more than 2 x 10(6) CD34(+)/kg to overcome myeloablative effects of skeletal irradiation. Nonhematologic side effects are minimal.	2
95. Bolger JJ, Dearnaley DP, Kirk D, et al. Strontium-89 (Metastron) versus external beam radiotherapy in patients with painful bone metastases secondary to prostatic cancer: preliminary report of a multicenter trial. UK Metastron Investigators Group. *Semin Oncol* 1993; 20(3 Suppl 2):32-33.	1	305	Compare efficacy of Sr-89 to EBRT in bone metastasis. EBRT was local (400X5) or HBI (6 Gy UHBI, 8 Gy LHBI) Sr-89 was 5.4 mCI.	• Sr-89=Local XRT at 3 months (61% some pain improvement vs 66% resp.; 44% "dramatic" pain improvement vs 36% resp.) • At 3 mo. 2/152 Sr-192 needed retreat vs 12/153 local XRT. • Similar results w. Sr-89 vs HBI: 66% improvement vs 63% HBI; 42% "dramatic" vs 43% HBI.	1
96. Franzius C, Schuck A, Bielack SS. High-dose samarium-153 ethylene diamine tetramethylene phosphonate: low toxicity of skeletal irradiation in patients with osteosarcoma and bone metastases. *J Clin Oncol* 2002; 20(7):1953-1954.	15 (Letter)	N/A	Comment on previous research (Anderson et al JNCO Jan 2002).	Case report of instance of 21-year old patient with osteosarcoma in which immediate pain relief was achieved with high-dose 153Sm-EDTMP.	4
97. McEwan AJ, Amyotte GA, McGowan DG, MacGillivray JA, Porter AT. A retrospective analysis of the cost effectiveness of treatment with Metastron in patients with prostate cancer metastatic to bone. *Eur Urol* 1994; 26 Suppl 1:26-31.	15 (CEA of patients in RCT)	29	A retrospective study was performed on the cost-effectiveness of treatment for advanced prostate cancer metastatic to bone.	Results suggest that treatment with Metastron can bring about reductions in management costs for patients with advanced prostate cancer and, coupled with the findings of the Trans Canada trial on the improvement in QOL for patients given Metastron, they add financial support to the clinical rationale for the use of Metastron for the palliative treatment of patients with bone metastases resulting from prostate cancer.	2

Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
98. Porter AT, McEwan AJ. Strontium-89 as an adjuvant to external beam radiation improves pain relief and delays disease progression in advanced prostate cancer: results of a randomized controlled trial. *Semin Oncol* 1993; 20(3 Suppl 2):38-43.	1	129	Report on benefits of Strontium-90 based on results from a clinical trial.	The addition of Strontium-90 to external beam radiation had no effect on survival. However, it has clear implications for improved palliation in advanced prostate cancer and may also impact positively on treatment costs.	2
99. Porter AT, McEwan AJ, Powe JE, et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. *Int J Radiat Oncol Biol Phys* 1993; 25(5):805-813.	1	126	Phase III Local XRT +/- strontium-89 (10.8 mCi).	Strontium-89 delays progression of bone metastasis and decreases need for retreatment.	
100. Robinson RG, Preston DF, Schiefelbein M, Baxter KG. Strontium 89 therapy for the palliation of pain due to osseous metastases. *JAMA* 1995; 274(5):420-424.	15	N/A	To present the current state of systemic radiopharmaceutical therapy for the palliation of pain in individuals with metastatic cancer and to evaluate the palliative effect and degree of hemotoxicity of strontium chloride 89 in patients with painful osteoblastic metastases primarily from prostate and breast cancer.	As many as 80% of selected patients with painful osteoblastic bony metastases from prostate or breast cancer may experience some pain relief following strontium-89 administration. In addition, as many as 10% or more may become pain free. Duration of clinical response may average 3 to 6 months in some cases. Hemotoxicity is mild. A decrease in treatment costs with administration of strontium-89 to patients with painful osteoblastic bony metastases from prostate cancer may occur.	2
101. Rogers CL, Speiser B, Ram PC, Shaw JA, Thomas TA. Efficacy and toxicity of intravenous strontium-89 for symptomatic osseous metastases. *J Brachytherapy International* 1998; 14:133-142.	2	60	Prospective study of efficacy and toxicity of strontium-89.	Percent reporting improvement: • 3-7 weeks: 69% • 7-11 weeks: 67% • 11-15 weeks: 48% There was no dose related response and no difference in response based on percent of red marrow involvement. Hemotoxicity (sometimes severe) is the major side effect.	3
102. Serafini AN, Houston SJ, Resche I, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol* 1998; 16(4):1574-1581.	1	118	To evaluate the effectiveness and safety of 153Sm-EDTMP in patients w painful bone metastasis secondary to other primary tumors.	A single dose of 1.0 mCi/kg of 153Sm-EDTMP provided relief from pain associated with bone metastases. Pain relief was observed within 1 week of administration and persisted until at least week 16 in the majority of patients who responded.	1

Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
103. Windsor PM. Predictors of response to strontium-89 (Metastron) in skeletal metastases from prostate cancer: report of a single centre's 10-year experience. *Clin Oncol (R Coll Radiol)* 2001; 13(3):219-227.	4	75	Retrospective analysis from patients with bone metastases secondary to prostate cancer who were treated with strontium-89 injection in a single centre.	It is suggested that early treatment with strontium-89 (Metastron) in patients with fewer bone metastases is more likely to be successful, with a longer time before further therapy required.	3
104. Bayouth JE, Macey DJ, Kasi LP, Fossella FV. Dosimetry and toxicity of samarium-153-EDTMP administered for bone pain due to skeletal metastases. *J Nucl Med* 1994; 35(1):63-69.	4	19	Palliation of bone pain in patients with cancer metastatic to bone is being evaluated in several cancer centers by the administration of the bone-seeking phosphonate EDTMP chelated with the beta particle-emitting radionuclide 153Sm.	Since the deviation of uptake between the four injections for a given patient (7.6% ID) was less than the deviation for all patients (16% ID), the initial dose may be used to estimate the skeletal uptake for the remaining doses. These radiation dose estimates permit patients at risk to be identified prior to reaching myelotoxicity and develop dose-response models. Thirteen patients (68%) reported significant pain relief from this radionuclide therapy. Bone pain appears to be alleviated by 153Sm-EDTMP with limited red marrow doses and no toxic effects in other organs.	3
105. Porter AT, Ben-Josef E. Strontium 89 in the treatment of bony metastases. *Important Adv Oncol* 1995:87-94.	7	N/A	Review of the research on use of Strontium 89 for bony metastases.	Recommend considering Strontium 89 in following circumstances: • Patients with widely metastatic disease as adjuvant to XRT. • Patients with one predominantly painful site. • Patients where XRT options have been exhausted. • Patients with life expectancy >3 months • Patients without evidence of epidural cord compression, fracture or mechanical instability. • Patients with good renal function.	3
106. Eary JF, Collins C, Stabin M, et al. Samarium-153-EDTMP biodistribution and dosimetry estimation. *J Nucl Med* 1993; 34(7):1031-1036.	2	52	Phase I dose-escalating study in which were treated with single doses of 153Sm-EDTMP for palliation of bone pain from metastatic prostate carcinoma.	Biodistribution data on this group of patients were acquired and showed rapid uptake of 153Sm-EDTMP into bone with complete clearance of nonskeletal radio toxicity by 6-8 hours.	2

Bone Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
107. Hanks GE. The crisis in health care cost in the United States: some implications for radiation oncology. *Int J Radiat Oncol Biol Phys* 1992; 23(1):203-206.	7	N/A	Reviews the increasing cost of medical care in the USA (13% of GNP in 1995) and the associated lack of access to care for 35 million citizens.	The portion of radiation oncology devoted to palliative care is discussed for its potential to reduce costs by $150-$250 million through the elimination of excessive treatments and thereby contribute to the solution of excessive cost of care.	3
108. Macklis RM, Cornelli H, Lasher J. Brief courses of palliative radiotherapy for metastatic bone pain: a pilot cost-minimization comparison with narcotic analgesics. *Am J Clin Oncol* 1998; 21(6):617-622.	4	66 patients with 131 treated sites	Clinical series to determine the effectiveness of brief courses of radiotherapy in reducing pain and to estimate cost data for a pilot comparison between radiotherapy and narcotic analgesics in patients with cancer.	The estimated cost per patient ranged from $1,200 to $2,500 for radiotherapy. This compares with an estimated cost of $9,000 to $36,000 for 9 months of narcotics.	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.