American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: **Bone Metastases**

Variant 1: **62-year-old man with prostate cancer. KPS 90. Two years after surgical resection of prostate and adjuvant hormonal therapy, rising PSA level found in routine follow-up. Asymptomatic bone metastasis in right femoral neck; lesion 1.5 cm in size; minimal invasion of bone cortex. No other metastatic disease.**

Treatment	Rating	Comments
Hormonal therapy (HT) and external beam radiation therapy (EBRT)	6	
HT alone	5	
EBRT alone	5	
Chemotherapy	1	
Systemic radiopharmaceuticals	1	
Surgical intervention	1	
Bisphosphonates	1	
Direct hospice placement	1	
Hospice after treatment of the femur	1	
Radiation Therapy Dose		
800 cGy/1 fraction	8	
2000 cGy/5 fractions	6	
3000 cGy/10 fractions	6	
3500 cGy/14 fractions	4	
4000 cGy/20 fractions	1	
Treatment Planning		
CT simulation	5	
Posterior field only	1	
Anterior-posterior fields	9	
Stereotactic radiosurgery (SRS)	1	
IMRT to the bone metastasis	1	
Proton therapy to the bone metastasis	1	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

(See Appendix 1 for additional information on expert panel's conclusions.)

Clinical Condition: **Bone Metastases**

Variant 2: **42-year-old woman with ER negative/PR negative breast cancer. KPS 90. Patient developed a symptomatic lytic bone metastasis in right femoral neck; the metastasis was 1.5 cm in size; minimal invasion of bone cortex. Diffuse asymptomatic bone metastases noted on bone scan with rising CEA.**

Treatment	Rating	Comments
Chemo and EBRT	6	
Chemo and bisphosphonates and EBRT	6	
Chemo and HT and EBRT	6	
Chemo and HT and bisphosphonates and EBRT	6	
HT alone	1	
Chemotherapy alone	1	
EBRT alone	1	
Systemic radiopharmaceuticals	1	
Surgical intervention	1	
Direct hospice placement	1	
Hospice after treatment of the femur	1	
Radiation Therapy Dose		
800 cGy/1 fraction	8	
2000 cGy/5 fractions	6	
3000 cGy/10 fractions	6	
3500 cGy/14 fractions	4	
4000 cGy/20 fractions	1	
Treatment Planning		
CT simulation	5	
Posterior field only	1	
Anterior-posterior fields	9	
Stereotactic radiosurgery (SRS)	1	
IMRT to the bone metastasis	1	
Proton therapy to the bone metastasis	1	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

(See Appendix 1 for additional information on expert panel's conclusions.)

Clinical Condition: **Bone Metastases**

Variant 3: **55-year-old woman with ER positive/PR positive breast cancer. KPS 80, with no prior history of spine radiation. Patient developed symptomatic vertebral metastases at T12, L1, and L2 without canal involvement. Diffuse asymptomatic bone metastases noted on bone scan with rising CEA.**

Treatment	Rating	Comments
HT and EBRT	8	
HT and bisphosphonates and EBRT	8	
Chemo and HT and EBRT	7	
Chemo and HT and bisphosphonates and EBRT	7	
Chemo and EBRT	6	
Chemo and bisphosphonates and EBRT	6	
HT alone	2	
Chemotherapy alone	2	
EBRT alone	2	If patient has had multiple chemo cycles and hormones, this may be appropriate.
Systemic radiopharmaceuticals alone	1	
Surgical intervention	1	
Direct hospice placement	1	
Hospice after treatment of the spine	1	
Radiation Therapy Dose		
800 cGy/1 fraction	7	
2000 cGy/5 fractions	7	
3000 cGy/10 fractions	7	
3500 cGy/14 fractions	7	
4000 cGy/20 fractions	1	
Treatment Planning		
CT simulation	8	
Posterior field only	5	
Anterior-posterior fields	6	
Posterior obliques	7	
Stereotactic radiosurgery (SRS)	1	
IMRT to the bone metastasis	1	
Proton therapy to the bone metastasis	1	
Rating Scale: **1=Least appropriate, 9=Most appropriate**		

(See Appendix 1 for additional information on expert panel's conclusions.)

Clinical Condition: **Bone Metastases**

Variant 4: **55-year-old woman with ER positive/PR positive breast cancer. KPS 80 and no prior history of spine radiation. Patient developed symptomatic vertebral metastases at T12, L1, and L2 with canal involvement; moderate weakness in the lower extremities. Diffuse asymptomatic bone metastases noted on bone scan with rising CEA. Past history includes multiple prior cycles of chemo/HT and bisphosphonates.**

Treatment	Rating	Comments
Surgical intervention and EBRT	8	
EBRT alone	6	
HT and EBRT	6	
HT and bisphosphonates and EBRT	6	
Surgical intervention and chemo and HT	6	
HT and bisphosphonates and systemic radiopharmaceuticals and EBRT	5	
Chemo and EBRT	5	
Chemo and bisphosphonates and EBRT	5	
Chemo and HT and EBRT	5	
Chemo and HT and bisphosphonates and EBRT	5	
HT alone	1	
Chemotherapy alone	1	
Systemic radiopharmaceuticals alone	1	
Surgical intervention alone	1	
Direct hospice placement	1	
Hospice after treatment of the spine	1	
Radiation Therapy Dose if Given Alone or with Chemo and/or HT and Bisphosphonates		
800 cGy/1 fraction	2	
2000 cGy/5 fractions	6	
3000 cGy/10 fractions	8	
3500 cGy/14 fractions	8	
4000 cGy/20 fractions	1	
If Radiation Therapy is Given after Surgical Resection		
800 cGy/1 fraction	1	
2000 cGy/5 fractions	1	
3000 cGy/10 fractions	8	
3500 cGy/14 fractions	8	
4000 cGy/20 fractions	1	
Treatment Planning		
CT simulation	8	
Posterior field only	7	
Anterior-posterior fields	7	
Posterior obliques	8	
Stereotactic radiosurgery (SRS)	1	
IMRT to the bone metastasis	1	
Proton therapy to the bone metastasis	1	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

(See Appendix 1 for additional information on expert panel's conclusions.)

Clinical Condition: **Bone Metastases**

Variant 5: **55-year-old patient with lung cancer. KPS 70. Prior external beam radiation for a Pancoast tumor, including vertebral levels C7-T4. Symptomatic vertebral metastases; paraspinous soft-tissue extension present from T6-10; spinal cord involvement and mild weakness. Diffuse metastatic disease noted on bone scan; multiple small liver metastases evident on CT of abdomen.**

Treatment	Rating	Comments
Hospice after treatment of the spine	7	
EBRT alone	6	
Chemo and EBRT	5	
Chemo and bisphosphonates and EBRT	5	
Direct hospice placement	2	
Chemotherapy alone	1	
Systemic radiopharmaceuticals	1	
Surgical intervention	1	
Chemo and bisphosphonates	1	
Radiation Therapy Dose		
800 cGy/1 fraction	2	
2000 cGy/5 fractions	6	
3000 cGy/10 fractions	8	
3500 cGy/14 fractions	7	
4000 cGy/20 fractions	1	
Treatment Planning		
CT simulation	8	
Posterior field only	7	
Anterior-posterior fields	7	
Posterior obliques	8	
Stereotactic radiosurgery (SRS)	1	
IMRT to the bone metastasis	1	
Proton therapy to the bone metastasis	1	
Rating Scale: **1=Least appropriate, 9=Most appropriate**		

(See Appendix 1 for additional information on expert panel's conclusions.)

Clinical Condition: **Bone Metastases**

Variant 6: **55-year-old patient with lung cancer. KPS 90. Prior external beam radiation for a Pancoast tumor, including vertebral levels C7-T4. Follow-up bone scan is negative; whole body PET/CT demonstrates uptake in liver, L3, L4, left humerus, and multiple ribs; CT biopsy of symptomatic left humerus confirms metastatic lung cancer. Radiograph of left humerus demonstrates lytic 1 cm lesion with 50% erosion of cortex. Serum calcium normal.**

Treatment	Rating	Comments
Surgical intervention and EBRT	8	
Hospice after treatment of the humerus	5	
Chemotherapy	1	
EBRT alone	1	
Systemic radiopharmaceuticals	1	
Surgical intervention alone	1	
Direct hospice placement	1	
If Radiation Therapy is Given after Surgical Resection		
800 cGy/1 fraction	1	
2000 cGy/5 fractions	5	
3000 cGy/10 fractions	8	
3500 cGy/14 fractions	7	
4000 cGy/20 fractions	1	
Treatment Planning		
CT simulation	5	
Posterior field only	1	
Anterior-posterior fields	8	
Posterior obliques	1	
Stereotactic radiosurgery (SRS)	1	
IMRT to the bone metastasis	1	
Proton therapy to the bone metastasis	1	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

(See Appendix 1 for additional information on expert panel's conclusions.)

Clinical Condition: **Bone Metastases**

Variant 7: **72-year-old man with non-small-cell lung cancer, 2 years status post right upper lobectomy. KPS 80. Previous radiation to the T5-T8 spine 10 months ago to 30 Gy in 10 fractions. Now with debilitating pain from recurrent disease at T7, no canal involvement. Diffuse asymptomatic bone metastasis, stable on bone scan. No visceral metastases.**

Treatment	Rating	Comments
Surgical intervention and systemic radiopharmaceuticals	9	
Surgical intervention alone	8	
Hospice after treatment of the spine	7	
Systemic radiopharmaceuticals alone	5	
Direct hospice placement	2	
Chemotherapy	1	
EBRT alone	1	
Bisphosphonates	1	
Surgical intervention and EBRT	1	
Surgical intervention and EBRT and systemic radiopharmaceuticals	1	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

(See Appendix 1 for additional information on expert panel's conclusions.)

Clinical Condition: **Bone Metastases**

Variant 8: **56-year-old woman with breast cancer diagnosed 3 years ago. KPS 90. Now with painful, solitary, biopsy-proven metastasis in the T4 vertebral body. No canal involvement. No other sites of metastatic disease. ER/PR positive.**

Treatment	Rating	Comments
Surgical intervention alone	8	
Surgical intervention and EBRT	8	
Surgical intervention and HT	8	
HT and EBRT	8	
HT and bisphosphonates and EBRT	8	
Chemo and EBRT	8	
Chemo and bisphosphonates and EBRT	8	
Chemo and HT and bisphosphonates and EBRT	8	
EBRT alone	6	
Chemo and HT and EBRT	6	
Surgical intervention and chemo and HT	5	
Surgical intervention and chemo and HT and bisphosphonates	5	
Surgical intervention and EBRT and chemo and HT	5	
Surgical intervention and EBRT and chemo and HT and bisphosphonates	5	
HT alone	2	
Chemotherapy alone	2	
Chemo and bisphosphonates	2	
Chemo and HT and bisphosphonates	2	
Systemic radiopharmaceuticals	1	
HT and bisphosphonates	1	
Direct hospice placement	1	
Hospice after treatment of the spine	1	
If Radiation Therapy is Given Alone or with Chemo and/or HT and Bisphosphonates		
800 cGy/1 fraction	2	
2000 cGy/5 fractions	5	
3000 cGy/10 fractions	8	
3500 cGy/14 fractions	8	
4000 cGy/20 fractions	1	

If Radiation Therapy is Given after Surgical Resection 800 cGy/1 fraction	1	
2000 cGy/5 fractions	5	
3000 cGy/10 fractions	8	
3500 cGy/14 fractions	8	
4000 cGy/20 fractions	1	
Treatment Planning CT simulation	9	
Posterior field only	4	
Anterior-posterior fields	7	
Posterior obliques	7	
Stereotactic radiosurgery (SRS)	1	
Stereotactic radiotherapy	7	
IMRT to the bone metastasis	5	
Proton therapy to the bone metastasis	1	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

Clinical Condition: **Bone Metastases**

Variant 9: **The following factors should be considered with regard to treatment recommendations for bone metastases.**

Factor	Rating	Comments
Extent of Disease		
Number of symptomatic bone metastases	9	
Number of asymptomatic bone metastases	8	
Presence of small lung/liver metastases	9	
Presence of large lung/liver metastases	9	
Presence of symptomatic visceral metastases	9	
Presence of brain metastases	9	
Presence of spinal cord compression	9	
Functional Status		
Karnofsky Performance Status	9	
Prognosis of >3months	8	
Prognosis of >6 months	9	
Prognosis of >12 months	9	
Mobility	9	
Pain	9	
Chronic use of opioid analgesics	9	
Jaundice	9	
Decreased cognitive function	8	
SVC syndrome	8	
Anorexia/nausea	8	
Ascites	8	
Pelvic mass	7	
Fatigue	6	
Dyspnea	2	
Presence of a feeding tube	1	
Lymphedema	1	
Prior Therapy/Tumor Type		
Progressive disease after >2 prior courses of chemotherapy/hormonal therapy for metastatic disease	9	
Progressive disease after prior radiation therapy for metastatic disease	9	
Progressive disease after prior bisphosphonate therapy for metastatic disease	1	
Progressive disease after prior systemic radiopharmaceutical therapy for metastatic disease	1	
Symptoms controlled where previously treated	8	
Disease controlled where previously treated	8	
Type of primary tumor	7	
Interval between primary diagnosis and development of metastatic disease	8	
Interval of metastatic disease progression	8	

Socioeconomic Issues		
Treatment related toxicity	9	
Time under therapy/prognosis ratio	9	
Time to benefit from palliative therapy/prognosis ratio	9	
Available social support	8	
Discussion about prognosis	8	
Patients wish for aggressive therapy	8	
Available clinical trials	8	
Advance directives	8	
Discussion about end of life issues during course of palliative care	8	
Transfer to hospice	8	
Cost to patient/family	8	
Societal cost	5	
Family's wish for aggressive therapy	4	
Insurance coverage for treatment	1	
Time to Benefit from Chemohormonal Therapy		
≤1 month	8	
≤2 months	8	
≤3 months	8	
≤6 months	8	
Time to Benefit from Bisphosphonates		
≤1 month	8	
≤2 months	8	
≤3 months	8	
≤6 months	8	
≤12 months	8	
≤18 months	8	
≤24 months	8	
Time to Benefit from External Beam Radiation Therapy		
≤1 month	8	
≤2 months	8	
≤3 months	8	
≤6 months	8	
Time to Benefit from Systemic Radiopharmaceuticals		
≤1 month	8	
≤2 months	8	
≤3 months	8	
≤6 months	8	
Rating Scale: **1=Least appropriate, 9=Most appropriate**		

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Summary of Literature Review

Treatments during the course of cancer are given with different intents. Antineoplastic therapy, literally defined as treatment for cancer, can be given throughout the course of care for cancer. Antineoplastic therapy may be given with curative intent, to prolong survival, or solely to relieve symptoms from cancer. Most cancer patients present with or will experience symptoms of the disease. Management of cancer-related and treatment-related symptoms is imperative during antineoplastic therapy, whatever the therapeutic intent.

There are generally two phases in the treatment of cancer metastases. Initially, when given with the intent to prolong survival, antineoplastic therapy is often aggressive, and has defined and potentially serious side effects. In the second phase, when cancer continues to progress, treatment should efficiently provide comfort to the patient with the fewest treatment-related side effects, recognizing that the patient will soon die from the disease.

Palliative care is defined as relieving the symptoms of cancer. Strictly speaking, symptoms of cancer can be palliated during curative cancer therapy. Palliative care should be distinguished from and is a continuum to end-of-life care, which is currently defined by Medicare hospice benefits as being administered in the last 6 months of life. From the perspective of the patient, reducing the burden of symptoms of cancer is one of the most significant accomplishments that health care professionals can achieve. From the perspective of those who care for the patient, suffering compounds the physical and emotional stress of witnessing the process of death. From a socioeconomic perspective, death is the most expensive process in health care; medical care at the end of life consumes 12% of the total health care budget, and 27% of the total Medicare budget is spent in the last 30 days of life [1]. The National Institutes of Health in 2004 estimated that the overall cost for cancer was $189.8 billion. This included $69.4 billion for direct medical costs, $16.9 billion resulting from lost productivity due to illness, and $103.5 billion caused by lost productivity due to death [2]. Ineffective palliative therapy, given by any means, is especially costly because of the potential toxicities of antineoplastic treatment and the continued need for analgesics and functional limitation related to unrelieved pain and disability [3,4].

Improving palliative care for cancer patients in the United States is one of the most pressing needs in oncology. Few therapeutic guidelines exist for the treatment of metastatic disease because of the complexity of the problem based on type of cancer and site(s) of involvement. The roles of systemic agents (including chemotherapy, hormonal therapy, bisphosphonates, and radiopharmaceuticals) and local therapies (including surgery and radiation), alone or in combination, still have not been fully defined. Part of the difficulty in determining the best multidisciplinary approach relates to the various types of clinical problems that require palliative care.

The treatment of bone metastases is one of the most common indications for palliative care, and it represents paradigm for the issues presented. Even among patients with bone metastases, a number of different clinical problems, like pathologic fracture and spinal cord compression, require different multidisciplinary considerations. Patient factors such as performance status influence decision-making. How therapies can be combined to achieve additive or synergistic effects while reducing treatment-related toxicities is an issue that especially needs to be addressed. Like the approach used in curative therapies combining chemotherapy and radiation, studies are needed that evaluate the combination of localized therapies, surgery and external beam radiation with systemic therapies (chemotherapy, hormonal therapy and bisphosphonates, and radiopharmaceuticals).

Under current practice, systemic chemo/hormonal therapy and bisphosphonates are usually administered when bone metastases are first diagnosed unless an impending pathologic fracture or spinal cord compression is identified. External beam radiotherapy is usually delayed until the metastatic disease progresses, causing significant pain or risk for pathological fracture or spinal cord compression. Use of radiopharmaceuticals is generally considered in a small fraction of patients with persistent multifocal sites of pain, or recurrence of pain in a previously irradiated site.

Prognostic Factors

Even in the most favorable situation for bone metastases, the median survival is 3 years or less. After bone metastases are diagnosed, the median survivals are 25 months with breast cancer, 6 months with prostate cancer,

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The American College of Radiology seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply society endorsement of the final document.

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and 3 months with lung cancer [5-7]. The distribution of bone metastases, as studied in prostate cancer, has prognostic significance. The rate of survival is significantly longer when the metastases are restricted to the pelvis and lumbar spine, and among patients who respond to salvage hormone therapy [8-10]. Any metastatic involvement outside the pelvis and lumbar spine results in lower rates of survival irrespective of response to salvage hormone therapy.

A bone scan index (BSI) was formulated based on the weighted proportion of tumor involvement in individual bones. The BSI was then related to known prognostic factors and survival in androgen-independent prostate cancer patients [11]. In multiple-variable proportional hazards analyses, only the BSI, age, hemoglobin level, and lactate dehydrogenase level were associated with survival. Survival times were 18.3 months for a BSI of <1.4%, 15.5 months for a BSI of 1.4 to 5.1%, and 8.1 months for a BSI of >5.1%. The site of the primary disease and the presence of a solitary metastatic site were predictive of a more prolonged survival [12-16]. The presence of bone metastases predicted for progression of disease to other sites, and bone metastases were the most common cause of cancer-related pain [6,8-10,17-19]. Elevation in the bone resorption marker, N-telopeptide [NTx], is another factor that has been associated with a 20-times higher risk for the development of a skeletal complication within 3 months, and shorter times to first disease progression and death [20,21]. Although not currently used in standard practice, these factors, which correlate with prognosis, may serve in the future as a surrogate for a staging system for metastatic disease so that palliative treatment is appropriate to prognosis based on the extent of disease.

The burdens imposed on those who care for cancer patients were detailed in a study of 988 terminally ill patients and 893 caregivers that was conducted in six randomly selected cities across the United States. Needs for transportation, nursing care, personal care and economic costs were evaluated [22]. The leading causes of terminal illness were cancer (51.8%), heart disease (18%), and chronic obstructive pulmonary disease (10.9%). The mean age was 66.5 years (range: 22-109 years), and 59.4% were at least 65 years of age. Expenditure of more than 10% of the household income on health care occurred in 35% due to substantial care needs; 16% of families had to take out a loan, spend their savings, or obtain an additional job to cover medical costs. Significant pain was noted by 50.2%, 17.5% were bedridden for more than half of the day, 70.9% had shortness of breath while walking one block or less, 35.5% had urinary or fecal incontinence, and 16.8% had depressive symptoms. In the previous 6 months, only 33.5% had not been hospitalized, 22.3% required a hospital stay that involved the intensive care unit, and 36.8% had undergone a surgical procedure. Patients with substantial needs were more likely to consider euthanasia, and administering care significantly impacted the life of over 35% of caregivers. Importantly, when physicians listened to the needs of patients and their caregivers, the caregivers had significantly fewer burdens of care. Only 28% of families felt burdened by the illness if the physician was involved in the needs of terminal care as compared to 42% whose physicians did not listen to the needs of the family [P=0.005].

A study by Stafford and Cyr involving more than 9,700 community-based Medicare beneficiaries found poorer health, more limitation on activities of daily living, and greater levels of health care utilization among the 1,647 individuals who had Cancer [23]. Significant debility was observed more frequently in lung, breast, prostate, and colon cancer patients. Lung, bladder and prostate cancers predicted for increased health care utilization, and lung cancer most frequently limited the activities of daily living.

The mean annual Medicare costs for lung cancer were more than twice those for colon, breast, and prostate cancers. Even though the decrease in functional capacity for cancer patients was generally not as prolonged as with other chronic diseases like arthritis, stoke and emphysema, the annual health care costs for cancer patients were greater than those for other chronic diseases [24].

The physical symptoms among 350 hospice inpatients with cancer correlated with patient characteristics, general condition, tumor location and medications. The mean number of symptoms correlated directly with the Karnofsky performance status (KPS); the KPS status was 10-20 with seven symptoms, 30-50 with six symptoms and ≥60 with four symptoms [25]. Quality-of-life measurements have also been shown to predict for survival and add to the prognostic information derived from the KPS and extent of disease. Among 208 patients with terminal cancer, the overall median survival was 15 weeks. Physical symptoms such as pain, dry mouth, constipation, change in taste, lack of appetite and energy, feeling bloated, nausea, vomiting, weight loss, and feeling drowsy or dizzy portended a poorer prognosis [12]. Shorter survival times were independently associated with the following factors: primary site (lung cancer vs breast and gastrointestinal cancers), liver metastases, comorbidities, weight loss of greater than 8 kg in the previous 6 months, and clinical estimation of a less than 2- month survival by the treating physician. Laboratory assessments showing serum albumin levels of less than 3.5 dg/L, lymphocyte counts of less than 1 x 10^9/L, and LDH levels of more than 618 U/L also were associated with a poor prognosis [26]. After these independent factors were accounted for in the analysis, other factors, such as performance status, did not independently affect the prognosis.

Pain represents a sensitive measure of disease activity [27-31]. Pain was reported to be the presenting symptom in 79% of 108 patients referred to an outpatient multidisciplinary bone metastases clinic. The time since diagnosis of the primary tumor ranged from 2 weeks to 23 years; the median time since diagnosis was 22 months,

and 30% of patients had been diagnosed within the past 6 months [32]. The median age of the population was 55 years, and 69% of the patients were less than 65 years of age. On average, pain was rated as moderate to severe in 79% and severe in 23% of patients; at its worst, pain was rated as severe by 78% and intolerable by 22% of the patients. Only 45% of patients experienced good relief from the prescribed analgesics, and 23% indicated that the prescribed analgesics were ineffective. Despite this, 21% of patients worked full-time and 6% were employed part-time; 13% were homemakers, and only 16% of patients considered themselves to be disabled.

Socioeconomic Impact of Metastatic Disease

Medicare costs are particularly high for cancer patients in the last 2 years of life, accounting for nearly 11% of annual Medicare expenses [33]. The average payments depend on type and stage of disease. The highest total Medicare payment from diagnosis to death is the highest for bladder cancer and the lowest for lung cancer because of the limited survival time associated with metastatic lung cancer [34]. During the last 6 months of life, however, the rates for administration of chemotherapy are the same for all types of tumors. Medicare data from Massachusetts in 1996 showed that chemotherapy was administered during the last 6 months of life in 33% of cancer patients, with 23% receiving chemotherapy in the last 3 months of life and 9% in the last month of life [35]. The Surveillance, Epidemiology and End Results Program data were similar among 28,777 patients over the age of 65 years that died within 1 year of a diagnosis of lung, breast, colorectal, or other gastrointestinal cancer between 1993 and 1996. Rates of chemotherapy administration increased from 28% in 1993 to 30% in 1996 [P=0.02]. A similar increase, from 14% to 19%, was noted among patients receiving chemotherapy in the last 2 weeks of life [36]. This was associated with a statistically increased number [7% vs 9%] of emergency department visits, hospital admissions, or admissions to the intensive care unit during the last month of life.

Benchmarking to avoid futile care and for more optimal utilization of health care resources at the end of life, it was considered that less than 10% of patients should receive chemotherapy in the last 14 days of life and that less than 2% of patients should start a new chemotherapy regimen in the last 30 days of life. Additionally, less than 4% of patients should have emergency room visits, hospitalizations, or intensive care unit admissions in the last month of life. More than half of cancer patients should be receiving hospice care, and less than 8% of cancer patients would die within 3 days of hospice admission [37].

Half of the costs of Medicare in the last year of life are incurred during the last 60 days of life [38]. Higher expenditures by Medicare have not always resulted in higher quality of health care, especially with regard to palliative care. Instead, health care spending often reflects health care delivery systems, the composition of the medical workforce, and the capacity constraints within the health care system [39].

Much controversy surrounds the use of bisphosphonates for bone metastases from a cost-effectiveness perspective. One study showed that the cost of pamidronate exceeded the cost saved by preventing adverse events. The projected net cost to prevent an adverse skeletal-related event (SRE) was $3,940 with chemotherapy and $9,390 with hormonal therapy [40]. The cost-effectiveness ratios were $108,200 with chemotherapy and $305,300 with hormonal therapy per quality-adjusted year. A cost analysis study in Canada showed similar findings. Over a 12-month time frame, the total costs in the pamidronate arm were 44% higher than in the placebo arm [41]. Without surgical intervention, pamidronate increased costs by $31,600 per quality-adjusted life year. When the cost of surgical intervention, required by 6% of the study group, was included, the use of pamidronate increased costs by $13,300 per quality-adjusted life year. Based on the number of breast cancer patients who would meet clinical indications to receive pamidronate, the added cost for bisphosphonates would exceed $10 million (Canadian) per year in Ontario.

Despite these economic issues, bisphosphonates have become the standard of care for breast cancer patients who have lytic bone metastases and who are receiving chemotherapy or hormonal therapy [42]. In a report of over 700 breast cancer patients randomized to receive chemotherapy alone or chemotherapy and bisphosphonates, bone metastases were first diagnosed 18 months before study, entry and about 70% of patients had bone as their only site of metastatic disease. This study demonstrated that the development of skeletal complications was delayed by bisphosphonates. With chemotherapy alone, skeletal complications occurred at 7.0 months vs 13 months with systemic therapy and bisphosphonates. With chemotherapy the proportion of skeletal complications was 56% vs 43% with chemotherapy and bisphosphonates [43,44]. With hormonal therapy alone, skeletal complications occurred at 7.0 months vs 10 months with a combination of hormonal therapy and bisphosphonates [43]. The proportion of skeletal complications was reduced from 67% with hormonal therapy alone to 56% with combined therapy. In both studies, the occurrence of nonvertebral pathologic fractures, surgery or radiation therapy, bone pain, and hypercalcemia were all significantly reduced with bisphosphonates. However, no survival advantage was observed in the bisphosphonate group; the median survival was 37 months. With extended follow-up, 78% of patients in both the bisphosphonate and placebo groups died because of progression of breast cancer before completing 24 months of treatment, with a median survival of about 18 months [45].

A review by Gainford et al [42] summarized the data on treatment with bisphosphonates. First, bisphosphonates are now considered an established standard of care for breast cancer patients with metastases. Second, randomized controlled trials confirm significant reductions in SREs with bisphosphonates. It was noted, however, that SREs exclude pain, immobility, analgesic

use and nonhospital costs like physical therapy. The definition of SREs in the literature is generally restricted to pathologic vertebral and nonvertebral fractures, spinal cord compression, surgery and radiotherapy for bone complications, and hypercalcemia. Third, previous trials contained highly selected patient populations who were most likely to benefit from treatment with bisphosphonates. Fourth, bisphosphonates work best in those patients with bone-only disease — namely, those who live long enough to gain benefit. Finally, bisphosphonates effects are time dependent; in terms of SREs with significant benefits only after 3 to 6 months of treatment. The following issues relative to efficacy, routine clinical practice, and cost must be considered.

Administration of bisphosphonates did not influence the level of pain relief in the Radiation Therapy Oncology Group (RTOG®) trial that compared a single 8 Gy fraction to 30 Gy in 10 radiation fractions of palliative radiation. The overall response rate was 66% for both treatment arms, and at 3 months 33% of all patients no longer required narcotic analgesics [46]. Only 14% of patients who no longer required narcotic analgesics, representing less than half of the complete responders in each radiation treatment arm, received bisphosphonates more than 30 days prior to the initiation of radiation therapy. The incidence of pathologic fracture was 5%, and median survival was 9 months; overall survival was 41% at 1 year and 22% at 2 years for both study arms.

Socioeconomic factors need to be considered in the treatment of metastatic cancer, since palliative care represents a significant percentage of the overall cost of cancer therapy. Up to two-thirds of health care costs are not reimbursed by insurance [47-57]. A survey conducted among 1,531 adults in the United States between April 25 and June 9, 2005 confirmed the pressing issue of health care costs [48]. Even though 61% of this group had health insurance coverage, 23% of Americans in this survey had problems paying medical bills in the previous year. Medical bills included physician charges [85%], lab fees [62%], and prescription drugs [56%]. Medical bills resulted in serious financial consequences over a period of 5 years for 19% of those surveyed, with 12% using "all or most" of their savings, 8% borrowing money or taking out another mortgage, and 3% declaring bankruptcy. Health care costs for 18% were the biggest monthly expense excluding rent or mortgage payments. Among the 16% of adults who tried to buy health insurance, 69% were unable to do so, with 72% citing cost of the insurance premiums as the barrier. Health insurance premiums rose 9.2% from 2004 to 2005, representing the first year of single-digit increases since 2000 and the second consecutive year when premiums rose less than they did the year before, but premiums have risen 73% since 2000, outpacing overall inflation and wages by six percentage points. The percentage of firms in the United States offering health care benefits fell from 69% in 2000 to 60% in 2005, while enrollment in health maintenance organizations fell from 25% to 21% [53]. About half of the four million individuals in the United States who file for bankruptcy each year cite medical costs as a contributing factor. Health care insurance at the time of diagnosis was available in three-quarters of these cases [49]. Related to this, involuntary gaps in insurance coverage occurred due to unaffordable premiums, patient or caregiver loss of employment, and lack of disability benefits or paid sick leave. Medicare Parts A and B cover less than half of medical care costs [51]. In 2005, national health care expenditures (NHE) represented 16% of gross domestic product. Out-of-pocket spending in 2005 was $249 billion and accounted for 12.6% of NHE. Total spending on prescription drugs increased 66% between 2000 and 2005 or 10.7% annually, while total spending on all health care expenditures grew 46.9% over the same time period, for an 8.08% annual rate [58].

The scope of the problem is enormous, especially for cancer treatment, and will only balloon with the demographics of an aging population. As health care resources continue to become more limited, our criteria for care must be better defined to avoid administration of therapy with limited benefit [59-66]. Leadership must come from health care professionals, as clinical trials and clinical practice increasingly interface with health care policy. Goals of therapy must remain clear for the benefit of the individual and all patients.

Goals of Palliative Care

In the United States, approximately half of patients who receive radiation therapy are treated with palliative intent. The goals of palliation include the relief of symptoms, if present, or the prevention of symptoms that are likely to occur in the future, referred to as prophylactic or prospective palliation [1]. Physicians need to develop treatment plans for patients with metastatic disease so the patients do not spend a disproportionate percentage of their survival time getting antineoplastic treatment. Palliative cancer treatment should be administered over the shortest period of time possible and should provide comfort to the patient with the fewest treatment-related side effects, allowing patients to use their remaining time, which may be more than a year, to attend to important personal matters and goals while they are still able to do so. Ineffective, futile therapies that incur morbidity and cost and provide little to no palliative benefit should not be administered.

Physicians must communicate what can reasonably be achieved with treatment. End-of-life issues addressing treatment during the last 6 months of life should be discussed with the patient and caregivers at some point during the course of palliative treatment to avoid potential difficulties arising from unrealistic expectations and underestimated toxicities from proposed treatments, and to determine and follow the patient's wishes [67-74]. The physician must acknowledge and compassionately discuss these issues with the patient and caregivers, and reassure the family that the patient will not be abandoned and that care will continue.

Role of Radiation in Palliative Care

Radiation therapy has contributed to improvements in quality of life. These contributions range from multidisciplinary therapies that preserve functional and esthetic integrity to strategies that avoid prolonged therapy, such as approaches used in brachytherapy, to pain management. Principles of quality of life that maintain functional integrity, reduce time under therapy, and prevent or reduce suffering are particularly important for patients with metastatic disease.

Palliative therapy for cancer has greater prominence as quality-of-life issues have gained recognition within cancer therapy. Systemic therapies, including bisphosphonates, are generally administered without interruption for metastatic disease. But systemic therapies for metastatic disease have had limited impact on overall survival. Symptom relief from systemic therapies is variable, and ongoing systemic therapies can cause significant toxicities that can result in hospitalization. Fatigue from uninterrupted therapy and from dealing with the hospital system can often consume the patient's remaining survival time. The current paradigm continuously administers systemic therapy and surgery or radiation therapy is generally used only to treat severe symptoms.

Instead of the current therapeutic paradigm, different multidisciplinary paradigms should be considered for palliative care. Consistent with perspectives to optimize quality of life, every modality used for palliative therapy must efficiently and effectively relieve cancer symptoms with the fewest possible side effects.

Underutilization of Palliative Radiation

Quality-of-life issues have driven much of the evolution of radiation therapy. Multidisciplinary approaches that include radiation therapy have allowed organ-sparing surgical approaches in head and neck cancer, sarcomas, and breast cancer. Radiotherapy has long been used to relieve symptoms of metastatic disease in every anatomic sight. The efficacy of palliative radiation in symptom relief is well documented and exceeds that of systemic therapies, which are administered to prevent disease progression. It is important to recognize that about 50% of patients will experience relief of pain just two weeks after completing palliative external beam radiation for bone metastases, and that more than 75% will have pain relief four weeks after completing radiation [46,75,76]. Likewise, systemic radiopharmaceuticals have comparable rates of pain relief, have no visceral toxicity, and are effective in preventing skeletal-related events.

More recently, palliative radiotherapy has been underutilized in the United States and in most developed nations in favor of systemic therapies. Although palliation traditionally has represented a large part of radiotherapeutic practice, radiation is generally considered to be an underutilized cost-effective treatment in palliative care. At the M.D. Anderson Cancer Center, about 25% of all radiation treatments were administered with palliative intent [77]. Consistent with radiotherapeutic practice in the United States, palliative radiotherapy for bone metastases was administered to approximately 25% of all radiotherapy patients in Sweden. However, this corresponded to only 10% of all Swedish cancer patients [78]. Since more than half of patients with prostate, breast, and lung cancer will develop symptoms from metastases, palliative radiation therapy is considered to be greatly underutilized since bisphosphonates have not been shown to reduce the need for analgesics to treat pain from symptomatic lesions.

Efficiency of Palliative Radiation Schedules

Improvements are needed to optimize each therapeutic approach. Palliative therapy is optimized as time under treatment is optimized. The time under radiation needs to be considered as the opportunity cost of palliative treatment [79]. If the median survival of a patient with bone metastases is 6 months (180 days), the patient will spend 0.6% of the remaining survival time under radiation treatment when a single fraction of radiation is given. If 10 radiation fractions are given, 8% of the remaining survival time, and if 20 fractions are prescribed, 16% of the remaining survival time will be consumed by radiation therapy. Even if retreatment with a second single fraction is required, the patient will continue to spend about 1% of the survival time under radiation therapy. For lung cancer patients with a 3-month survival rate, 1% of the remaining time is spent with a single fraction of radiation, compared to 16% if 10 fractions are given, or 30% if 20 fractions are prescribed.

Single Fraction Radiation

A single large radiation fraction has been shown to be as effective in relieving pain as other radiation schedules that have more treatments. In more than 10 prospective randomized trials conducted in Europe, no difference was reported in how quickly symptoms resolved or in the duration of pain relief when a single dose of radiation was compared a radiation schedule with multiple radiation fractions [79-92]. In each case, symptom relief lasted 3 months in 70% of patients, 6 months in 37%, and 12 months in 20% of cases. As in the RTOG® study, about 69% responded at 4 weeks, and response rates plateaued, totaling 80%, at 8 weeks. Complete response rates after a single 8 Gy fraction totaled 15% at 2 weeks, 23% at 4 weeks, 28% at 8 weeks, and 39% at 12 weeks postradiation. Because survival is determined by the location and number of sites of metastatic disease rather than the number of radiation fractions used for a localized area of disease, overall survival rates for a single fraction of radiation are equivalent to those achieved by a course of palliative radiation with multiple fractions.

A meta-analysis of 18 prospective randomized trials evaluated three different palliative radiation dose schedules. These schedules included different doses of single-fraction radiation therapy, comparisons of single-fraction versus multiple- fraction radiotherapy, and comparisons of different doses of multiple-fraction radiotherapy. A comparison of all these radiation schedules showed no difference in response rates based on radiotherapy dose [92]. The median period of pain

relief ranged between 11 and 24 weeks, and no difference was found in the 1-to-4 week median time to pain relief. There was a significant difference between remineralization of lytic lesions at 6 months follow-up was 173% after 30 Gy in 10 fractions compared to 120% after a single 8 Gy fraction, but the pretreatment and post-treatment risk of pathological fracture was not determined [87]. Factors found retrospectively to influence the use of a single versus multiple radiation fractions for bone metastases included patient age, performance status, anatomical site, and year of radiation therapy [88,92]. While trials using a single fraction radiation included vertebral metastases, many advocate a more protracted radiation schedule for vertebral metastases to avoid symptoms, such as nausea, resulting from exit dose to adjacent normal structures.

A RTOG® prospective randomized trial consisted of 949 breast and prostate cancer patients comparing 30 Gy in 10 fractions to a single 8Gy fraction for bone metastases. The pretreatment characteristics of the 847 analyzable patients were equally balanced between treatment arms. They included 56% having a weight-bearing painful site, 72% having severe pain, 27% who were receiving bisphosphonates, and 57% with a solitary painful site. Acute toxicity was mild, with a total of only two patients experiencing a grade-4 toxicity and 24 with a grade-3 toxicity [46]. But the 30 Gy arm had significantly more grade-2 to grade-4 toxicity, 17% vs 10%. Median survival was 9 months, with 41% of patients alive at 1 year. No difference was observed in pain relief at 3 months. The rates of complete pain relief (CR) and partial pain relief (PR) were 15% and 50%, respectively, for the 8 Gy arm, and 18% and 48%, respectively, for the 30 Gy arm. At 3 months, one-third of patients no longer required analgesics.

A shorter radiation schedule, like a single fraction, is advantageous for patients with poor prognostic factors. *First*, it is easier for patients with a poor KPS to complete therapy. *Second*, response and survival rates are equal for single and multifraction therapy at 3 months because median survival is less than 6 months among patients with poor prognostic factors and average around 24 months among patients with metastatic disease [79,82,86,90-92]. This is an important consideration when the number of weeks of survival is evaluated relative to the number of weeks receiving palliative treatment. *Third*, the option of retreatment after a single fraction of radiation may also provide an advantage among patients with good prognostic factors as a means to periodically reduce tumor burden and control symptoms in noncritical anatomic sites. *Fourth*, a single fraction of radiation is more cost-effective. The cost of radiation therapy is reduced by 41% with the use of a single fraction when compared to a 10-fraction course of palliative radiation. The cost of radiation therapy is less expensive than the continued cost of analgesics, and an analysis of a Dutch prospective study showed cost benefit for a single-fraction of radiation when compared to multiple radiation fractions, even when retreatment was included in the single-fraction arm [79,87,91].

The previous ACR Appropriateness Criteria® on *Bone Metastases* stated:

> "Although the RTOG® over 10 years ago demonstrated that 20 Gy in 5 fractions gave similar results to more protracted regimens, most clinical trials investigating schedules with less than 10 fractions have been performed outside of the United States. Consequently, most radiation oncologists in the United States lack experience with daily doses of 4 Gy or more. To determine the optimal dose fractionation scheme, more emphasis should be placed on the life expectancy of the patient. A dose of 20 Gy in 5 fractions or even more rapid schedules is acceptable in patients with short life expectancy (ie, less than 3 months). Unfortunately, there is little agreement or information on objective correlates to life expectancy. Thus, performance status was used as a surrogate for this measure by the panel. Based on these observations, at least two areas of research should be considered: 1) measurement of the efficacy of a 1- to 5-fraction course of palliation and 2) the definition of a group of patients with a very limited life expectancy, say 3 months, in whom a short course of palliative radiation might be considered. This research can best be done in a cooperative group setting and the conclusions would represent an important contribution to issues related to health care cost containment."

The RTOG® [46] clinical trial has been completed, yet, there is little change in clinical practice in radiation oncology with regard to fractionation schedules used for palliative radiation, especially of sites outside the vertebral axis. The argument that American radiation oncologists lack experience in administering a single fraction of radiation is not appropriate since radiation oncologists have sought training and have introduced highly technical advancements, such as intensity-modulated radiation therapy and brachytherapy, into their practices. Additionally, practices have introduced multimodality therapeutic approaches based on survival benefits, such as chemoradiation for cervical cancer, from clinical trials with far fewer patient numbers. Based on multiple prospective randomized clinical trials conducted by cooperative groups both in Europe and the United States, a single fraction of radiation is appropriate for nonvertebral metastases. More prolonged radiation schedules and more complex radiation treatment planning may be appropriate for vertebral metastases to reduce toxicity to adjacent structures such as the larynx, esophagus, and stomach.

Radiopharmaceuticals

High rates of pain control have also been achieved with radiopharmaceuticals [46,93-103]. Given as a convenient single intravenous administration on an outpatient basis, (another systemic treatment for multifocal bone metastases), radiopharmaceuticals also have a response

time of about 4 weeks, with effective palliation of pain lasting more than 6 months in 60% to 80% of patients with breast and prostate cancers. The half-life of Strontium 89 in normal bone is about 14 days, and in the diseased bone it is 51 days. Pain control has been correlated with objective evidence of response, and has been documented by reductions in alkaline phosphatase levels and decreased uptake in metastatic lesions on sequential bone scans.

Because the activity of radiopharmaceuticals is limited to bone, there are no toxicities other than the possibility of a flare in bone pain that is self-limited and predictive of response, and myelotoxicity that results in less than a 25% decline of the initial platelet and white blood cell counts. Myelotoxicity is usually transient and represents the only significant toxicity associated with radiopharmaceuticals [104,105]. Myelotoxicity with radiopharmaceuticals results from extensive chemotherapy or radiation for tumor, and is more pronounced in patients with pretreatment platelet counts of $\leq 60 \times 10^3$, white blood counts of $\leq 2.5 \times 10^3$, or $\geq 30\%$ involvement of the red marrow-bearing bone by tumor [103,106]. Using a patient-centered endpoint of pain relief instead of SRE, benefit was documented when radiopharmaceuticals were combined with localized external beam radiation to symptomatic sites, resulting in better rates of pain relief and delay progression of disease in prospective randomized clinical trials.

Pathological Fracture

No new findings regarding the use of palliative radiation to prevent or treat pathologic fracture have been contributed to the literature since the last ACR Appropriateness Criteria® on *Bone Metastases* review. The conclusions of that guideline stand:

> "The quality of life of patients who undergo surgical fixation of metastases within long bones before the occurrence of fracture is considerably better than those with pathologic fractures. If lesions can be measured, those measuring 3 cm or destroying 50% of the cortex of tubular bone in a single radiograph should be considered for fixation before irradiation because of the tendency to fracture either during or shortly after treatment."

While these conclusions relate to the surgical fixation of long bones relative to the administration of radiation therapy, this same recommendation should also be applied to patients receiving systemic therapies.

Spinal Cord Compression

This guideline also concurs with the conclusion from the previous appropriateness guideline regarding management of spinal cord compression:

> "Most cord compressions from vertebral metastases extending into the epidural space can be managed with high-dose corticosteroids and radiation. Surgery is indicated when vertebral body collapse causes mechanical impingement on the spinal cord or nerve roots, often associated with a history of progressive neurologic deficit over 72 hours or less. Surgery should also be considered if the diagnosis is in doubt, if stabilization is necessary or if radiotherapy has already been given to the same area."

Spine metastases cause significant pain and can result in irreversible paralysis. Patients with known vertebral metastases require frequent clinical evaluation to identify any change in symptoms and/or radiographic findings suggesting risk for spinal cord compromise. Early detection of vertebral compromise is paramount to preventing an oncologic emergency with severe pain and neurologic compromise from spinal cord compression. Emergent oncologic care involves steroids and either surgical decompression or radiation therapy. Efforts to prevent spinal cord compression due to progression of bone metastases through systemic therapies continue.

Radiation remains an important modality in the treatment of vertebral metastases. A number of clinical, prognostic, and therapeutic factors must be considered to determine the most optimal treatment regimen. Effort should be undertaken in radiation treatment planning to reduce toxicities, like esophagitis and nausea, from palliative radiation of the spine. Symptoms that persist after palliative radiation should be evaluated. Persistent symptoms after radiation may signal progression of disease in the treated area, and possible extension of disease outside the radiation portal, especially if there was an associated paraspinal mass. Pain may also persist due to reduced cortical strength after treatment of spinal metastases that can result in vertebral compression or stress microfractures. Vertebral compression due to reduced cortical strength after radiation therapy may also require surgical intervention to prevent spinal cord injury.

Cost-Effectiveness of Palliative Radiation

Approximately 300,000 patients nationwide receive palliative radiation costing $900 million per year. About 100,000 patients receive curative radiation therapy costing a total of $1.1 billion per year; the total cost of curative and palliative radiation therapy to the nation is less than the costs associated with the administration of growth factors to prevent anemia during administration of systemic chemotherapy [3,107].

Compared to analgesic therapy alone, radiotherapy for bone metastases effectively relieves symptoms and is both efficient and cost-effective. The costs of radiotherapy were evaluated among 66 patients who underwent palliative radiation totaling 30 Gy in 10 fractions (72%) or 20 Gy in 5 fractions. Pain scores decreased about 4 points (0 to 10 scale) after radiotherapy from a median level of 5.58 before radiation to 1.55 after treatment [108]. Likewise, incident-related pain with movement decreased 5 points from 7.32 before treatment to 1.94 after treatment. The estimated cost of radiotherapy ranged from $1,200 to $2,500 per patient. With durable pain relief for 9 months, the estimated cost of analgesics over the same time period would have totaled $9,000 to $36,000. A brief course of radiation therapy proved to significantly reduce pain and was cost-effective when

compared with the continued need for analgesics, and presented an important consideration for the treatment of hospice patients.

Cost-benefit analysis has also suggested an advantage to the administration of strontium-89, with reductions in costs of hospitalization for tertiary care [97,98]. The cost of a single dose and the administration of a radiopharmaceutical or a palliative course of external beam radiation is significantly less than the costs incurred by either prolonged administration of either intravenous or oral bisphosphonates.

Summary

The previous ACR Appropriateness Criteria® on *Bone Metastases* published in 2003 primarily addressed issues related to radiation fractionation, and acknowledged the emerging use of bisphosphonates into clinical practice. This guideline addresses the issues that have continued to loom over the American health care system. While new therapeutic options are needed in cancer therapy, what is also needed is better utilization of health care resources. With regard to the emergence of bisphosphonate therapy, the previous guideline stated that:

> "Bisphosphonates therapy is expensive, must be continued indefinitely and does not abolish the risk of skeletal complications, but merely delays their onset. It is unlikely that studies on bisphosphonates and radionuclides will be reserved for patients who are refractory to chemotherapy or have too many lesions for local field radiation therapy. Already many investigators have shown a prejudice to use these systemic agents earlier in the course of disease or as a prevention measure. Unfortunately this will impede the initiation of studies that will help to establish which patients should qualify for these systemic treatments. To complicate matters even further is the hypothesis that earlier treatment with these agents will be more cost-effective, despite the initial higher cost."

The development of therapies such as bisphosphonates is important to advancing options for palliative care. However, studies should define clear indications and the specific benefit to the patient. Trials should determine when to start and stop the therapy, and the appropriate patient populations to receive the therapy. Toxicities, such as renal impairment and osteonecrosis of the jaw with bisphosphonates, need to be clearly evaluated relative to those of other therapeutic modalities and overall survival. Cost-utility analyses need to be performed for palliative care endpoints that include efficacy, efficiency, and functional outcomes compared to other available therapies. Clinical trials that include these criteria are critical to future practice guidelines development.

The key question is not what *can* be done, but what *should* be done. In sum, more may not be best for the patient. It is recognized that health care professionals are facing tremendous conflicting pressures in clinical practice. Among these pressures are often unrealistic expectations for outcomes demanded by an internet-savvy public, changing rules, and declining reimbursement for inpatient and outpatient care from Medicare and other payors, pressures to see more patients with a declining workforce, and litigation. While warnings regarding a crisis in American health care have been discussed for almost two decades, the time clock is running out. The demographics in America are not amenable to a short-term fix, since the baby-boomer population is beginning to reach retirement age. Currently, more than two-thirds of the Federal budget is designated for entitlements, leaving little ability to increase further spending on health care, which now already consumes over 15% of the American gross domestic product [58].

It is clear that health care practices that do not provide added clinical benefit, defined as improving the patient's quality of life, must be abandoned. An additional 2 weeks of overall survival while suffering from disease does not represent clinical benefit. More consideration must be given to expenditures of time, energy, and the personal finances of the patient and caregivers. It must be recognized that each intervention a patient undergoes requires effort and has side effects that consume, often precious, time in recovery.

The treatment of bone metastases represents a paradigm for evaluating palliative care in terms of symptom relief, toxicities of therapy, and the financial burden to the patient, caregivers, and society. Despite enormous expenditures to treat metastases, overall survival rates have not changed significantly, patients continue to suffer symptoms of the disease, and aggressive therapeutic approaches often are pursued throughout the course of metastatic disease that incur toxicity in approximately 25% of patients. This approach is inconsistent with the goals of palliative care, which should efficiently provide comfort, using antineoplastic therapies and/or supportive care with the fewest treatment-related side effects, recognizing that the patient will die from the disease. Research is necessary in therapeutic strategies that explore efficient multidisciplinary schedules for bone metastases to relieve symptoms and the burdens of therapy. Given the extreme pressures on the American health care system, changes in clinical practice are also necessary. These changes in should be supported by guideline development, and by education of health care professionals and the American public.

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Supporting Document(s)

- ACR Appropriateness Criteria® Overview
- Evidence Table

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Appendix 1.

This section is intended to impart the thoughts of the expert panel in reaching its conclusions based on commonly encountered clinical scenarios. Therapeutic options available for consensus for each of the clinical scenarios included the following ***and every potential combination*** of the following modalities:

- Hormonal therapy alone or hormonal therapy and bisphosphonate therapy alone
- Chemotherapy alone or chemotherapy and bisphosphonate therapy alone
- External beam radiation alone
- Systemic pharmaceuticals alone
- Surgical intervention alone
- Direct hospice placement

If external beam radiation was recommended, the dose fractionation schedule was examined relative to whether radiotherapy was administered alone or in combination with any other therapeutic modality. The radiotherapy fractionation schedules considered included:

- 800 cGy / 1 fraction
- 2000 cGy / 5 fractions
- 3000 cGy / 10 fractions
- 3500 cGy / 14 fractions
- 4000 cGy / 20 fractions

Radiation treatment planning options considered included the following:

- CT simulation
- Posterior field only
- Anterior-posterior fields
- Stereotactic radiosurgery
- IMRT
- Protons

The factors considered in rating the fractionation schemes and treatment options included adherence to prospective randomized data, patient convenience, risk of side effects, ability to retreat the same area if necessary, and cost. In all cases, CT simulation was considered extremely prevalent in practice; few practices continue to even have traditional simulation machines available. CT simulation is performed, therefore, by default. Advantages were also identified for CT simulation in treatment of spinal lesions for accurate coverage of the involved vertebrae, and if paraspinous extension exists. CT simulation also allows the possibility for more conformal radiation that reduces morbidity to adjacent uninvolved mucosal structures, like the esophagus.

Three rounds of independent voting were conducted. This was followed by a conference call to discuss the rationale underlying the recommendations. Consensus was found for each of the following clinical scenarios:

Variant 1: **62-year-old man with prostate cancer. KPS 90. Two years after surgical resection of prostate and adjuvant hormonal therapy, rising PSA level found in routine follow-up. Asymptomatic bone metastasis in right femoral neck; lesion 1.5 cm in size; minimal invasion of bone cortex. No other metastatic disease.**

The most appropriate therapy was considered to be hormonal therapy and localized external beam radiotherapy to prevent progression that results in pain and risk for pathologic fracture (rated as 6).

- Alternatives included hormone therapy alone or radiotherapy alone (both rated as 5).
- Chemotherapy, systemic radiopharmaceuticals, surgical intervention, bisphosphonates, and hospice placement were all considered inappropriate (rated as 1).

The most efficient radiotherapy doses were rated the highest or most appropriate based on multiple prospective randomized trials that demonstrated comparable rates of response, and that allowed reirradiation later in the course of the disease. Protracted courses of radiotherapy were not considered appropriate. Treatment portals using AP-PA technique were highly recommended (rated as 9), while conformal radiotherapy techniques, including IMRT and protons, were rated as inappropriate (rated as 1).

Variant 2: **42-year-old woman with ER negative/PR negative breast cancer. KPS 90. Patient developed a symptomatic lytic bone metastasis in right femoral neck; the metastasis was 1.5 cm in size; minimal invasion of bone cortex. Diffuse asymptomatic bone metastases noted on bone scan with rising CEA.**

It is recognized that this patient, despite her good performance status, has highly aggressive diffusely metastatic breast cancer for which there is no cure. Aggressive chemotherapy, with or without hormonal therapy, will likely be prescribed, given current practice patterns, in an attempt to slow the trajectory of the disease. Assessment of the morbidity of aggressive systemic therapy relative to the limited extension of survival, and the quality of life during the course of systemic therapy, using an analysis such as quality-adjusted life years [QUALYs], is outside the purview of this report.

Current practice patterns also would likely include bisphosphonates, in addition to systemic antineoplastic therapy. With current practice patterns, bisphosphonates are generally also prescribed with systemic antineoplastic therapy because of the diffuse bone metastases, even though the symptomatic lesion is primarily lytic and bisphosphonates impart no survival advantage. The goal of bisphosphonate therapy is to delay or prevent the need for localized external beam radiotherapy through indefinite monthly intravenous administration of the agent. Recognized potential systemic toxicities include renal dysfunction and osteonecrosis of the jaw.

Acknowledging that the goal of bisphosphonates is to delay or avoid the administration of radiotherapy, there still was full consensus that external beam radiotherapy would provide benefit to any prescribed systemic antineoplastic regimen. It was the opinion of the group that radiotherapy would provide prompt relief of pain to the symptomatic lesion and reduce the risk of subsequent pathologic fracture. There was consensus that radiotherapy is often delayed while awaiting response to bisphosphonate therapy. Additionally, based on published reports, guidelines, and clinical experience, pain relief with bisphosphonate therapy is often incomplete. During this delay, patients continue to require analgesics over a prolonged period of time for pain management, and the lesion in the femur remains at risk for pathologic fracture. Surgical intervention, systemic radiopharmaceuticals, and external beam radiotherapy given as a single modality were considered inappropriate.

Irrespective of the systemic therapy prescribed, the most efficient radiotherapy course, field arrangement, and modality were advocated for the reasons listed in the first case.

Variant 3: **55-year-old woman with ER positive/PR positive breast cancer. KPS 80, with no prior history of spine radiation. Patient developed symptomatic vertebral metastases at T12, L1, and L2 without canal involvement. Diffuse asymptomatic bone metastases noted on bone scan with rising CEA.**

Like the case above, there is a localized symptomatic region, and diffuse asymptomatic bone metastases. Differences exist in that this patient is older, with a slightly lower performance status, and vertebral involvement. Again, it was recognized that this patient has incurable disease.

The use of external beam radiotherapy with hormonal therapy, with or without bisphosphonates, was rated highly (rating of 8). Hormonal therapy, like localized radiotherapy, incurs limited morbidity while treating symptomatic disease, and limiting consequential disease progression. The addition of chemotherapy to external beam radiotherapy and hormonal therapy, with or without bisphosphonates, was rated less favorably (rating of 7) due to the considered morbidity of chemotherapy, limited survival benefit, and quality of life during the course of chemotherapy. In this ER positive and PR positive patient, not using hormonal therapy along with chemotherapy (+/- bisphosphonates) and external beam radiotherapy was the least favored therapeutic alternative and was rated as 6. Systemic radiopharmaceuticals and surgical intervention were not considered appropriate.

Especially in this symptomatic spine lesion where disease progression under systemic therapy alone could incur the risk of spinal cord compression, the benefit of adding external beam radiotherapy to any systemic regimen was again emphasized. Consensus was reached that if external beam radiotherapy was not administered to the spine, then very close monitoring of the patient would be required to monitor for early symptoms of spinal cord compression.

The radiotherapy dose fractionation prescribed varied from those for long bones. Fractionation schedules ranging from a single 8 Gy fraction, to 35 Gy/14 fractions were all rated as 7, while 40 Gy/20 fractions was considered inappropriate due to the protracted length of therapy. CT simulation, to accurately include the involved vertebrae and account for body habitus in radiotherapy dose calculation, was rated as 8. Common radiotherapy field arrangements, AP/PA (rated 6) and PA alone (rated 5) were considered appropriate. Posterior oblique treatment approach was most favored (rated 7) as it is an easy, relatively conformal dosimetric approach that can reduce the volume of and the radiotherapy dose administered to the esophagus within the radiotherapy field. However, more sophisticated conformal approaches like stereotactic radiosurgery, IMRT, and protons were not considered necessary.

Variant 4: **55-year-old woman with ER positive/PR positive breast cancer. KPS 80 and no prior history of spine radiation. Patient developed symptomatic vertebral metastases at T12, L1, and L2 with canal involvement; moderate weakness in the lower extremities. Diffuse asymptomatic bone metastases noted on bone scan with rising CEA. Past history includes multiple prior cycles of chemo/HT and bisphosphonates.**

This ER/PR positive breast cancer patient presents with early spinal cord compression and diffuse asymptomatic bone metastases in other locations after multiple prior cycles of chemo/HT and bisphosphonates.

Due to the presenting weakness, surgical decompression followed by radiotherapy is advocated (rated 8) if possible. If surgery is not an option, emergent radiotherapy (rated 6) should be initiated alone or with further hormonal therapy, since there is limited treatment related morbidity with hormonal therapy. Given progression of disease under prior extensive systemic therapy, consensus was less favorable (rated 5) for continuing systemic therapy. This reflected concerns regarding the futility of continuing systemic therapy after the development of an early spinal cord compression and progressive disease despite prior aggressive therapy. Surgical intervention (rated 8) and radiotherapy and radiotherapy alone (rated 6), without the addition of systemic therapies, were considered highly appropriate, and more appropriate than further systemic therapy. It is important to note that hospice placement was not recommended and that supportive care was to be continued with the treating oncologists.

The most appropriate radiotherapeutic schedules were 30Gy/10 fractions or 35 Gy/14 fractions (each rated 8) for this case of early spinal cord compression. A more abbreviated alternative schedule of 20 Gy/5 fractions could be considered if the patient's clinical condition was poor; however, if surgery was performed, 20 Gy/5 fractions was not an acceptable radiotherapy schedule. The extremes of a single 8 Gy fraction, due to the spinal cord compression, and a protracted course of 40 Gy / 20 fractions were not considered appropriate.

The benefits of CT simulation and radiotherapy field arrangement were consistent with those in the previous case. Likewise, stereotactic radiosurgery, IMRT, and proton therapy were considered inappropriate.

Variant 5: **55-year-old patient with lung cancer. KPS 70. Prior external beam radiation for a Pancoast tumor, including vertebral levels C7-T4. Symptomatic vertebral metastases; paraspinous soft-tissue extension present from T6-10; spinal cord involvement and mild weakness. Diffuse metastatic disease noted on bone scan; multiple small liver metastases evident on CT of abdomen.**

It was the consensus of the group that this poor-prognosis patient should receive localized palliative radiotherapy to prevent paralysis followed by hospice placement (rated 7). Direct hospice placement was not advocated due to the logistical difficulties in coming for radiotherapy and the reimbursement restrictions in most hospice benefits, including Medicare. Due to the spinal cord compression and the bulk of disease with paraspinous involvement, CT simulation and multifraction radiotherapy are advocated as in the first case, ranging from 20 Gy/5 fractions to 35 Gy/14 fractions. Concerns were expressed regarding the futility of administering further chemotherapy; although rated 5, this rating reflected current practice trends.

Variant 6: **55-year-old patient with lung cancer. KPS 90. Prior external beam radiation for a Pancoast tumor, including vertebral levels C7-T4. Follow-up bone is negative; whole body PET/CT demonstrates uptake in liver, L3, L4, left humerus, and multiple ribs; CT biopsy of symptomatic left humerus confirms metastatic lung cancer. Radiograph of left humerus demonstrates lytic 1 cm lesion with 50% erosion of cortex. Serum calcium normal.**

Surgical intervention followed by external beam radiotherapy was recommended (rated 8) given the high performance status and morbidity of pathologic fracture due to pain and function. Because of often restrictive hospice benefit plans noted above, hospice referral depends on the patient's clinical condition, including the potential development of symptoms in the lumbar spine, after the recommended surgery and radiotherapy.

Since surgery was recommended, postoperative multifraction radiotherapy, ranging from 20 Gy/5 fractions to 35 Gy/14 fractions, was recommended. A single 8 Gy fraction and 40 Gy/20 fractions were not considered appropriate. CT simulation was rated as 5, since this is often the only simulation unit available in most radiotherapy practices. Anterior/posterior portals were the only treatment portals recommended. Conformal radiotherapy techniques, like IMRT and protons, were not recommended.

Variant 7: **72-year-old man with non-small-cell lung cancer, 2 years status post right upper lobectomy. KPS 80. Previous radiation to the T5-T8 spine 10 months ago to 30 Gy in 10 fractions. Now with debilitating pain from recurrent disease at T7, no canal involvement. Diffuse asymptomatic bone metastasis, stable on bone scan. No visceral metastases.**

This case brought forward the issue of reirradiation of the spine. There was consensus that reirradiation using external beam therapy should not be pursued, and that techniques like proton therapy and IMRT are not appropriate based on the debilitating pain that would make sustained positioning unbearable for the patient.

Surgery could provide rapid relief of debilitating pain. Since there was no spinal canal involvement, systemic radiopharmaceuticals should be given either as an adjuvant or alone if surgery is not possible based on comorbidities.

Concern was again raised regarding the futility of systemic therapies in the postoperative setting, given the primary histology and overall poor prognosis.

CONCERNS

- Radiotherapy is underutilized to relieve the suffering related to bone metastases.
- More abbreviated radiation fractionation schedules, like a single 8 Gy fraction, are appropriate for treating uncomplicated metastases in long bones. Multifraction radiotherapy is recommended for metastases involving the spine. Sophisticated radiotherapeutic techniques, like protons and IMRT, are not appropriate for treating bone metastases.
- Beneficial radiotherapy is often delayed or avoided in favor of systemic bisphosphonates and/or chemotherapy. Concerns exist regarding the potential for pathologic fracture and spinal cord compression while delaying radiotherapy to symptomatic lesions.
- Although widely administered to treat bone metastases, these systemic therapies often incur morbidity while eventual disease progression is certain, with limited gains in overall survival. Quality-adjusted life year evaluations are needed to determine the potential benefits of systemic therapy and localized radiotherapy at specific points during the trajectory of metastatic disease.
- Hospice and supportive care, rather than aggressive therapies, should be more widely integrated into the care of patients with bone metastases. Hospice benefit plans need to allow palliative radiotherapy to overcome reimbursement barriers to administration.