

RADIATION THERAPY ONCOLOGY GROUP

RTOG 97-14

RANDOMIZED TRIAL OF PALLIATIVE RADIATION THERAPY FOR OSSEOUS METASTASES: A STUDY OF PALLIATION OF SYMPTOMS AND QUALITY OF LIFE

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SCHEMA

S	<u>Painful Site(s)</u>	R	<u>Arm 1:</u> 3.0 Gy x 10 Fractions
	1. Solitary		Total Dose : 30.0 Gy in two weeks
T	2. Multiple	A	
R	<u>Treatment Site</u>	N	
	1. Weight bearing		<u>Arm 2:</u> 8.0 Gy x 1 fraction
A	2. Non-weight bearing	D	Total Dose: 8.0 Gy single dose
T	<u>Worst Pain Score (Brief Pain Inventory BPI)</u>	O	
	1. 5-6		
I	2. 7-10	M	
	3. < 5 with \geq 60mg/day morphine p.o.		
F		I	
	<u>Receiving Pamidronate/Biphosphanates</u>		
Y	1. No	Z	
	2. Yes	E	

Eligibility: (See Section 3.0 for details)

- Histologically-proven breast or prostate malignancy.
- Radiographic evidence of bone metastasis with pain at that site (*painful metastases to skull, hands, and feet are not eligible*).
- Life expectancy of at least 3 months.
- Karnofsky Performance Score \geq 40, age \geq 18.
- BPI score \geq 5 or BPI score < 5 with \geq 60 mg of morphine (*or equivalent*) per day.
- No introduction of systemic therapy within 30 days of randomization. See Section 3.1.6.
- No prior radiotherapy or palliative surgery to the painful site.
- No systemic radio-isotopes (*e.g. Sr89*) in past 30 days.
- Not previously randomized to this study.
- Signed study-specific consent form.

Required Sample Size: 938

**4/1/99
4/30/01**

RTOG Institution # _____

RTOG /NCCTG 97-14

ELIGIBILITY CHECK (4/30/01)

RTOG Case # _____

(page 1 of 2)

Other Seq # _____

- _____(Y) 1. Is there histologic confirmation of a primary tumor of breast or prostate origin?
- _____(Y) 2. In the estimation of the investigator, does the patient have a life expectancy ≥ 3 months?
- _____(Y/N) 3. Has the patient completed the "Brief Pain Inventory" questionnaire scoring ≥ 5 ?
_____(Y) If the score is < 5 , is the patient taking ≥ 60 mg morphine (or equivalent, See Appendix VI) per day?
- _____(N) 4. Is there evidence of painful metastases to the skull, feet, or hands?
- _____(Y) 5. Is there radiographic evidence of bone metastases?
- _____(Y) 6. Is there pain associated with the positive radiographic site?
- _____(Y) 7. Was the radiographic study performed within 8 weeks prior to randomization?
- _____(N) 8. Is there impending fracture or evidence of pathologic fracture at the treatment site?
- _____(N) 9. Is surgical fixation of the treatment site planned?
- _____(N) 10. Has the treatment site received prior radiation or surgery?
- _____(N) 11. Has the patient received any systemic radioisotopes within the past 30 days?
- _____(Y/N) 12. Is the patient currently receiving systemic treatment, i.e. chemotherapy, hormonal therapy or immunotherapy?
_____(N) If yes, has the systemic therapy started within the 30 days prior to randomization?
- _____(N) 13. Is there clinical or radiographic evidence of spinal cord compression or cauda equina effacement?
- _____(≥ 18) 14. What is the patient's age?
- _____(≥ 40) 15. Karnofsky Performance Status.
- _____(Y/NA) 16. For a female patient within childbearing age, has a pregnancy test has been done within the past 7 days with a negative result?
- _____(N) 17. Is the patient already registered to this study?

(continued on next page)

RTOG Institution # _____

RTOG /NCCTG 97-14

ELIGIBILITY CHECK (4/30/01)

RTOG Case # _____

(page 2 of 2)

Other Seq # _____

The following questions will be asked at the time of randomization:

- _____(Y) 1. Was the eligibility checklist completed?
- _____(Y) 2. Is the patient eligible?
- _____ 3. Provide the date the study-specific consent form was signed (*must be prior to randomization*).

Patient's Name

Verifying Physician

Patient ID #

Referring Institution # (*if different*)

Specify the extent of the painful site(s):

- solitary
- multiple

Is the treatment site:

- weight bearing
- non-weight bearing

Report the BPI Score (*worst*):

- five to six
- seven to ten
- less than five

Is the patient receiving Pamidronate/Biphosphanates?

- no
- yes

Birthdate

Sex

Race

Social Security Number

Zip Code (*9 digit if available*)

Method of Payment

Will any component of the patient's care be given at a VA or military facility?

Treatment Start Date

Treatment Assignment

Completed by _____

Date _____

1.0 BACKGROUND AND SIGNIFICANCE

Palliative treatment is a significant portion of cancer care, with an estimated \$900 million spent each year on palliative radiation therapy.¹ A substantial proportion of that expenditure is for palliation of painful osseous metastases. Radiation therapy is quite effective in providing relief from painful bone metastases. Almost 90% of patients will experience improvement in their pain, with complete pain relief in about half of the treated patients.^{2,3} There is disagreement as to the most effective treatment schedule and total dose. Randomized trials have previously shown that a shorter course of radiation therapy may give substantial pain relief, perhaps the equivalent of that seen with longer treatment courses.^{4,7} This remains controversial, so much so that a recent consensus meeting on the treatment of bone metastases concluded with no significant recommendations except that "the relationships between radiotherapy dose and response duration in terms of pain relief and bone healing are poorly defined and require further investigation."⁸ Longer courses of treatment to higher total doses remain the most commonly used schedules in the United States. In a survey of 268 radiation oncologists in the United States, the physicians were asked about the management of a patient with bone metastases from breast cancer. The respondents recommended a median dose of 30 Gy given in 10 fractions; none recommended fewer than 7 treatments.^{9,10}

A Radiation Therapy Oncology Group (RTOG 74-02) multicenter trial compared differing dose levels of radiation therapy for palliation of bone metastases.⁵ Patients in that study had one or more painful osseous metastases of the femur, humerus, pelvis, thoracic or lumbar spine. A subjective scoring system of pain severity (*none = 0, mild = 1, moderate = 2, severe = 3*) and frequency of pain (*no pain = 0, occasional = 1, intermittent = 2, constant = 3*) was used to determine a "pain score". Similarly a scoring system for pain medication (*none = 0, analgesic = 1, mild narcotic = 2, strong narcotic = 3*) and frequency of medication administration (*none = 0, less than daily = 1, once per day = 2, more frequently than once per day = 3*) was used to determine a "narcotic score". By this scoring system, the only patients eligible for the study were those with a high pain score (*at least moderate pain occurring at least intermittently*) or a high narcotic score (*at least a mild narcotic used once or more per day*). Patients with a solitary osseous metastasis were randomized to either 4050 rad (cGy) in 15 fractions in 3 weeks (*270 cGy per fraction*) or 2000 cGy in 5 fractions over one week (*400 cGy per fraction*). Patients with multiple metastases were randomized to one of four regimens: 3000 cGy in 10 fractions over 2 weeks (*300 cGy per fraction*), 1500 cGy in 5 fractions over 1 week (*300 cGy per fraction*), 2000 cGy in 5 fractions over one week (*400 cGy per fraction*), and 2500 cGy in 5 fractions over 1 week (*500 cGy per fraction*). There were 750 patients entered into the multiple metastasis randomization of whom 613 (82%) were considered evaluable. Overall, 89% (547/613) eventually experienced at least minimal relief of pain, with 53% obtaining complete relief and another 30% experiencing partial relief. There was no significant difference in pain relief rates among the differing treatment schedules. There were no differences found among the four treatment groups with respect to promptness of minimal relief, but there were differences in the promptness of complete relief, with the fastest relief seen in the 1500 cGy treatment and the slowest in the 2500 cGy treatment. There was no significant difference in duration of minimal or complete pain relief among the four groups, or in the proportion of patients with relapse of pain. No significant difference was found in the post-radiotherapy occurrence of pathologic fracture among the four groups (5-9%). In the group with solitary metastases, 266 patients were entered onto the study, but only 146 (55%) were considered evaluable. Most of the patients considered non-evaluable (84/120) were excluded because of misclassification as having a solitary metastasis.¹¹ There was no difference between the two treatment groups in terms of minimal, partial or complete pain relief. A trend toward more prompt minimal pain relief was found in the 2000 cGy treatment arm ($p=0.06$). There was no difference in duration of pain relief nor in the proportion of patients with relapse of pain. There was a significantly higher incidence of pathologic fractures in the 4050 cGy treatment arm (18% vs. 4% in the lower dose group, $p=0.02$). For the entire group of patients in this study, both with solitary and multiple sites of metastases, patients with breast or prostate primary sites experienced more frequent minimal or complete pain relief, had fewer relapses of pain and had longer durations of minimal or complete pain relief compared to patients with lung or other primary sites. Patients with the most severe pain prior to treatment (*highest pain scores*) were significantly less likely to have minimal or complete relief of pain compared to patients with lower initial pain scores. The use of chemotherapy or steroid therapy during the on-study period was not found to have a significant effect on pain relief. A criticism of this study has been that the pain was scored by the treating physician rather than the patient, which may have biased the results.^{3,7} Another criticism is that the accrual of only slightly more than 1000 patients from 39 institutions took 4 years, suggesting that most of the eligible patients were not entered on the study.

Blitzer re-analyzed the same data by combining the solitary and multiple metastasis groups and performed a stepwise logistic regression.¹¹ The endpoints used that he examined included improvement in narcotic score, improvement in combined pain and narcotic scores, and incidence of retreatment of the same site. He found that the number of fractions of radiation used was significantly correlated with retreatment given, complete pain relief before retreatment, and complete relief by combined pain/ narcotic score. His conclusions were that the protracted course of treatment was associated with improved outcome, producing more pain relief than short courses of treatment. This re-analysis can be criticized on several points, and Blitzer conceded in the discussion section of the paper that "analyz[ing] the solitary and multiple groups together ... is not necessarily correct." The protocol allowed retreatment of the same site 4 weeks after completion of the initial course of radiotherapy if the patient had not achieved complete pain relief. The groups receiving the lowest doses in each arm of the study had the highest rates of retreatment, a point used by Blitzer to show that these treatment schemes were not as effective as more protracted treatments. The difference in the rate of retreatment, however, came primarily from two of the 39 participating institutions, possibly reflecting an institutional bias rather than a difference in treatment outcome.¹²

Price et al. from the Royal Marsden Hospital compared a single treatment of 8 Gy to a "conventional" course of 30 Gy in 10 fractions in a randomized prospective trial of radiation for painful bony metastases.⁴ Assessment of response to treatment was subjective, measured by a pain chart completed by the patient. The single fraction was as effective at palliating symptoms as the more protracted course, with no difference in promptness of pain relief, response rate or duration of pain relief between the 2 groups. The overall response rate was 85% with 27% complete pain relief, identical between the two groups. Neither skeletal site of treatment nor primary site/histology was associated with any difference in outcome. The same group tried a smaller single dose of 4 Gy in a phase II trial, with a 5% complete response rate and an overall 43% response rate.¹³ Hoskin et al. reported a subsequent randomized prospective trial from the same institution comparing 8 Gy in a single treatment to 4 Gy, also in one treatment.¹⁴ There were 133 patients in the 8 Gy treatment group and 137 in the 4 Gy group. There was a significant difference in the rate of response favoring the 8 Gy treatment (*69% at 4 weeks compared to 44% in the lower dose group*). The proportion achieving complete response was nearly identical between the two groups (*39% vs. 36%*). No significant differences were seen in response rates of patients with differing primary sites. Retreatments were given more frequently in the 4 Gy group (*20% vs 9%*). Even with the responses from the retreated patients included, the overall response in the 8 Gy group remained superior at 12 weeks after the initial treatment. In this study, the patients completed a pain chart on a weekly basis rather than on a daily basis (*as had been done on the 30 Gy vs. 8 Gy prior trial*). With this modification, patient compliance with completing the pain charts was improved from 38% to 75%.

Madsen compared 24 Gy in 6 fractions to 20 Gy in 10 fractions, with identical response rates between the two groups.⁶ Cole compared a single dose of 8 Gy to 24 Gy given in 6 fractions in a smaller randomized trial, evaluating pain relief and toxicity.¹⁵ No statistically significant difference was found between the two groups, although 25% of the single fraction group required retreatment to the same site. The single treatment group also experienced nausea more frequently (*77% vs. 33%*). A recently reported Danish study evaluated 30 Gy in 10 fractions versus 15 Gy in 3 fractions (*Rasmussen*). No difference in pain relief, impairment in activity or level of medication required was found between the two groups. Pain relief was evaluated using a simple scoring system similar to the RTOG 74-02 scale, with physician interview of patients. Good or complete pain relief was noted in approximately half of the patients in both groups by one month, and 66-69% by 3 months. The only quality of life variable assessed (*other than pain*) was level of activity. Severe or moderate limitation of activity was documented in 72% prior to the start of irradiation, which decreased to 33% of patients at 3 months.

Components of the physical dimension common to both quality of life and pain include physical symptoms, functional status and fatigue. Components of the psychological dimension common to both quality of life and pain include emotional well-being and spirituality. Components of the social dimension common to both include social functioning, role functioning and treatment satisfaction (*including bureaucratic "red tape" and financial concerns*). Measurement of these factors will be assessed using a general quality of life instrument, the Functional Assessment of Cancer Therapy (*FACT*). Cleeland and others suggest two dimensions specific to pain: sensory, the facets of which include severity, location, quality, chronicity and degree of relief due to therapy; and reactive, the facets of which include anxiety, depression, suffering, the meaning of pain in relation to disease progression and perceived availability of relief.^{16,32} Melzack and Casey suggest a third dimension, cognitive-evaluative, the facets of which include attitudes and beliefs about pain.³³ This clinical trial will attempt to measure the first two dimensions. The

Brief Pain Inventory (*BPI*)³⁴ will be used to assess severity, location, chronicity, degree of relief due to therapy, perceived availability of relief, depression and suffering. The 0 Pain Worst 10 assessment of this index is the most highly correlated to interference with enjoyment of daily activities, and has breakpoints that correlate with levels of interference.²⁹ The scale is 0-10, and there are breakpoints between scores of 4 and 5 and between 6 and 7, indicating that mild pain correlates with scores of 1-4, moderate pain with 5-6 and severe pain with scores of 7-10.

The previous studies of radiation therapy for osseous metastases have primarily focused on pain relief in the 3 months following treatment. While this is obviously quite important, there are other significant issues that have not been addressed with these studies. Pain relief may be affected by multiple factors, including mood and insight.² The impact of the treatment on quality of life has not been investigated other than in terms of pain relief. The Functional Assessment of Cancer Therapy (*FACT*) scale was developed and validated at Rush-Presbyterian-St. Luke's, and is used to evaluate quality of life issues in cancer patients.¹⁷ The *FACT-G* scale is a 33 item generic core reflecting symptoms or problems associated with malignancies. This scale, as well as 6 disease-specific subscales, were developed using 135 patients with advanced cancer, and then validated on a second sample of 630 patients with a variety of cancers at different stages. Patients rate all items using a 5-point rating scale ranging from "not at all" to "very much." The measure yields information about total quality of life, as well as information about the dimensions of physical well-being, social/family well-being, relationship with doctor, emotional well being, functional well-being, and disease-specific concerns. Six additional experimental items request information regarding how much each dimension affects QL, using a "0" (*not at all*) to "10" (*very much so*) rating scale. The *FACT-G* scale is able to distinguish Metastatic from non-metastatic disease, $F(1,334)=5.38$, $p<.05$. It also distinguishes between stage I, II, III and IV disease, $F(3,308)=2.94$, $p<.05$, and between inpatients and outpatients from different centers, $F(2,411)=17.0$, $p<.001$. On the *FACT-G*, sensitivity to disease status was restricted to the Physical ($p<.01$) and Functional ($p<.001$) subscales. Concurrent validity is supported by strong Pearson correlations with the Functional Living Index - Cancer (.79) and a patient-completed version of the QL Index (.74). Initial evidence for construct validity is supported by: 1) moderate to high correlations with mood state as measured by the Taylor Manifest Anxiety Scale (.57) and a shortened version of the Profile of Mood States (.69); 2) moderate correlation with activity level (*negative direction of coefficient because of reverse scaling*) as measured by the Eastern Cooperative Oncology Group five-point rating (-.56), and a small correlation with social desirability as measured by a shortened version of the Marlowe-Crowne Social Desirability Scale.²²

A concern with quality of life studies is that inadequate numbers of patients will complete the quality of life instruments. Two recent studies suggest that it is possible to achieve a high level of participation in a quality of life study for cancer patients. In trials by the International Breast Cancer Study Group, patients were asked to complete questionnaires on quality of life and psychological distress at 3 month intervals.¹⁸ Seventy-two percent have completed all the requested questionnaires for the first nine months after entry onto the study. In a separate, randomized trial assessing pamidronate treatment in patients with metastatic breast cancer, patients were asked to complete a quality of life questionnaire every 3 months.¹⁹ With a median follow-up of nearly 18 months, evaluable questionnaires have been returned for more than 80% of the data collection intervals.

The previous trials of palliative radiotherapy for bone metastases have not included the evaluation of the economic impact of the treatment. The economic impact can include a comprehensive cost-effectiveness analysis which would entail estimating the comparative cost per quality adjusted life year of alternative therapies.²⁰ This approach has become a common approach to evaluating a number of health technologies, programs and procedures.^{21,22} Because so little is known about the costs associated with these alternative treatments, a more modest approach of estimating and comparing costs of illness appears more appropriate.²³⁻²⁶ These trials comparing palliative therapy should be ideal for the development of an appropriate database for estimation and comparison of costs.

Direct costs consist of all facility, supplies, medications and physician charges related to the administration of the radiotherapy. It is expected that the direct costs of the single treatment will be less than the direct costs of two weeks of treatment. In addition, all follow-up medical treatments related to the cancer or palliative irradiation, including cancer-related hospitalizations, visits to other physicians, services by other health care professionals, and the costs of medications will be included as direct costs. Little data is available to allow estimation of the differences (*if any*) in these direct costs. Other health care costs not related to treatment of the cancer or treatment related complications will not be considered (*e.g., the costs associated with an acute myocardial infarction in a patient who received*

palliative hip irradiation would not be considered but the costs of rehydration for a patient with esophagitis following treatment of the thoracic spine would be included).

Exact dollar costs will vary depending on many factors, including insurance status and geographic region. To eliminate these biases, data will be collected on the resources used rather than the direct costs of the medical treatments. These surrogates for costs will be compared using relative comparisons such as Resource-Based Relative Value Scales. As an example, the direct treatment resources of the two treatment schedules for a course of treatment to a single site using no customized blocks ("*simple*" treatment) are compared in the following table:

CPT code	Description	Total RVUs	8 Gy in 1		30 Gy in 10	
			# of charges	Total RVUs	# of charges	Total RVUs
99243	Consultation	2.54	1	2.54	1	2.54
77261	Treatment plan	2.10	1	2.10	1	2.10
77280	Simulation	4.59	1	4.59	1	4.59
77300	Basic calculations	2.30	1	2.30	1	2.30
77417	Verification port film	0.60	1	0.60	2	1.20
77403	Daily treatment	1.80	1	1.80	10	18.00
77420	Weekly management	2.44	0	0	2	4.88
77431	Short course treatment management	2.74	1	2.74	0	0
77336	Continuing physics support	3.02	0	0	1	3.02
	Total RVUs			16.70		38.66

The RVS scales will be used to model costs, and the actual data of resources used (*collected on all patients*) and actual costs (*collected from selected institutions*) will be used to estimate the model. Survival will be adjusted for quality of life outcomes by using a utility weight ranging from 0 (*dead*) to 1 (*healthy*). Utilities will be assessed using the Health Utilities Index (*HUI*).

Physician estimates of survival times are often inaccurate, usually being over optimistic. In several studies as many as 83% of survival predictions were overly optimistic, by 3 weeks to 3 months on average.^{28,30,38} Performance status has been positively correlated with survival times in several studies, but in other studies the clinical prediction of survival has been more accurate.^{39,40} Multiple prognostic factors have correlated with survival times, typically with different factors found to be predictive of survival in each series. Some of these factors include dyspnea, anorexia, weight loss, xerostomia, dysphagia, immobility, decubitus ulcers, pain, delirium, vomiting. Psychosocial factors and quality of life indices have been predictive of survival time in some series but not in others. The FACT yields information about total quality of life, as well as information about the dimensions of physical well-being, social/family well-being, emotional well being, functional well-being, and disease-specific concerns. Since this instrument measures so many of the factors previously noted to correlate with duration of survival, this scale may be a better correlate of longevity than clinical prediction or Karnofsky performance status. A clinical estimate of survival will be required for entry onto this study, and this study will allow comparison of clinical prediction, Karnofsky performance status and the FACT QOL scale to determine which (*if any*) are predictive of survival duration.

2.0 OBJECTIVES (4/1/99)

- 2.1** To determine whether 8 Gy in a single fraction provides equivalent pain and narcotic relief compared to 30 Gy in 10 fractions for patients with painful bone metastases.
- 2.2** To determine the frequency and duration of pain relief and narcotic relief for each of the two treatment arms.
- 2.3** To determine the effect on quality of life measures for each of the two treatment arms.
- 2.4** To determine the incidence of pathologic fracture within the treatment field for 8 Gy in a single fraction compared to 30 Gy in 10 fractions.
- 2.5** To evaluate resource utilization and create a model to compare resources/costs for each of the two protocol treatment arms.

- 2.6 To correlate survival time with physician prediction of survival, Karnofsky performance status, and FACT quality of life score to determine which gives the best estimation of actual survival time in this group of patients.
- 2.7 To determine cost-effectiveness of therapies in terms of cost/quality adjusted life years.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (4/1/99, 4/30/01)

- 3.1.1 The patient must be 18 years of age or older.
- 3.1.2 The patient must have histologically proven malignancy of breast or prostate. Histologic diagnosis may be established from needle biopsy, bone marrow biopsy, cytology, or a surgical biopsy or resection.
- 3.1.3 Radiographic evidence of bone metastasis is required and must have been performed within 8 weeks prior to randomization. Acceptable studies include plain radiographs, radionuclide bone scans, computed tomography scans and magnetic resonance imaging. Other studies may be acceptable with the approval of the principal investigator.
- 3.1.4 Eligible Treatment Sites Are:
- | | |
|----------------------------------|--|
| <i>Weight bearing sites:</i> | 1. pelvis (<i>excluding pubis</i>) |
| | 2. femur |
| | 3. sacrum and/or sacroiliac joints |
| | 4. tibia |
| <i>Non-weight bearing sites:</i> | 5. up to 5 consecutive cervical, thoracic or lumbar vertebral bodies |
| | 6. lumbosacral spine |
| | 7. up to 3 consecutive ribs |
| | 8. humerus |
| | 9. fibula |
| | 10. radius ± ulna |
| | 11. clavicle |
| | 12. sternum |
| | 13. scapula |
| | 14. pubis |
- If multiple sites are treated, the treatment site is included as weight-bearing if any of the sites include the pelvis, sacrum, femur or tibia.
- 3.1.5 The patient must have pain which appears to be related to the radiographically documented metastasis in the opinion of the treating physician, and the decision has been made by the responsible clinician that a course of palliative external beam radiation therapy is appropriate treatment. Patients must have a “Worst Pain Score” of ≥ 5 on a scale of 10 (*as scored on the Brief Pain Inventory [BP] question #3: 0 = no pain; 10 = worst possible pain*) or if BPI is < 5 , must be taking narcotic medications with a daily morphine equivalent dose ≥ 60 mg *p.o.* (*see Appendix VI for conversion tables*).
- 3.1.6 Patients receiving systemic therapy are eligible for this study as long as there has been no introduction of any systemic therapy within the 30 days prior to entry into this study. For example, the patient is eligible if continuing on a systemic agent or there is a change from one systemic agent to another. The patient is ineligible if the systemic agent commences within the 30 days prior to registration. This includes hormonal therapy, chemotherapy, and immunotherapy.
- 3.1.7 Patients must have an estimated life expectancy of 3 months or greater, as estimated by the responsible clinician.
- 3.1.8 Patients will be eligible for treatment of multiple osseous sites only if those sites can be included in no more than three treatment sites. For patients with painful metastases that are contiguous but do not fit into the definition of a site listed above, those patients will still be eligible but will be considered to have two treatment sites. For example, a patient with a lesion of T4, T7 and T9 would be eligible but would be considered as two treatment sites since more than five consecutive vertebral bodies would be treated. These lesions could be treated with one field, even though the treatment is coded as two sites.
- 3.1.9 Signed study-specific informed consent prior to randomization.
- 3.1.10 Karnofsky Performance Status ≥ 40 .
- 3.1.11 Patient must have completed all pretreatment evaluations in Section 4.0.

3.2 Ineligibility Criteria (4/1/99, 4/30/01)

- 3.2.1 Metastases to skull, feet and hands are not eligible treatment sites for this study. Patients with nonpainful metastases to skull, hands, or feet but who have painful eligible sites are eligible for this study.

- 3.2.2 Patients will be ineligible if the painful area has received prior radiation therapy or prior palliative surgery. Patients may have received prior palliative or primary radiotherapy or surgery to other parts of the body, as long as the current painful bone metastasis was not in the prior radiation fields and has not received prior palliative surgery. Patients will also be ineligible if there is pathologic fracture or impending fracture of the treatment site or planned surgical fixation of the bone.
- 3.2.3 Patients with vertebral metastases and with clinical or radiographic evidence of spinal cord or cauda equina compression/effacement.
- 3.2.4 Hematologic primary malignancies.
- 3.2.5 Patients receiving systemic radiotherapy (*Sr-89*) within 30 days prior to randomization.
- 3.2.6 Patients receiving treatment to non-eligible sites (*skull, hands, feet, or with impending pathologic fracture or with spinal cord/cauda equina compression*) are not eligible for this study.
- 3.2.7 Previously randomized to this study.

4.0 PRETREATMENT EVALUATION

4.1 Required Tests Prior to Randomization: (4/1/99)

- 4.1.1 Histologic diagnosis of the primary site.
- 4.1.2 History and physical and Karnofsky performance status.
- 4.1.3 Radiograph report documenting bone metastases within eight weeks prior to randomization.
- 4.1.4 Completed Brief Pain Inventory including worst pain score (*BPI question #3*) and pain medication (*narcotic*) usage information from the BPI.
- 4.1.5 Negative pregnancy test for females of childbearing potential within seven days prior to randomization.
- 4.1.6 Physician prediction of patient survival.
- 4.1.7 Consultation by radiation oncologist.
- 4.1.8 Health Utilities Index (*HUI*) and Quality of Life (*FACT-G*) are mandatory pre-treatment.

5.0 REGISTRATION PROCEDURES

5.1 Randomization

It is the responsibility of each participating Cooperative Group to decide which of its member institutions may participate in this protocol. Each participating Cooperative Group must ensure that IRB approval was obtained prior to accession of cases. Patients who meet the eligibility criteria in Section 3.0, sign the consent form, and pass the pretreatment evaluation, will be entered into the study prior to any protocol therapy. RTOG Members will call (215) 574-3191, 8:30 am - 5:00 pm, Eastern Time. The following information will be required at the time of patient entry:

- Institution's Name and RTOG Institution Identification Number (*when calling RTOG*)
- Patient's name (*or initials*) and ID Number
- Verifying Physician's Name
- Eligibility Criteria Information
- Stratification Information
- IRB Approval Date
- Demographic Data
- Treatment Start Date

5.2 NCCTG Institutions (9/8/98)

A signed 310 form must be on file for this study at the NCCTG Randomization Center before a NCCTG institution may enter a patient.

To register a patient, fax a completed eligibility checklist (507/284-0885) to the NCCTG Randomization Center between 8:00 a.m. and 3:00 p.m. central time, Monday through Friday. The NCCTG Randomization Center will obtain and confirm all eligibility criteria. The NCCTG Randomization Center will then contact RTOG Headquarters to register the patient. The treatment assignment and case number from RTOG will be relayed to the registering institution by NCCTG. RTOG will send a Confirmation of Registration and a Forms Due Calendar to NCCTG Randomization Center who will forward this information to the participating institution.

6.0 RADIATION THERAPY

6.1 Treatment Plan

- Arm 1: 3.0 Gy x 10 fractions to 30.0 Gy total dose in two weeks.
- Arm 2: 8.0 Gy in 1 fraction to 8.0 Gy total dose.

- 6.2** Simulation of treatment fields is required prior to the first treatment. Prior to the first treatment, there must be an acceptable simulator and portal film documenting that the treatment site is adequately covered and verified by the treating radiation oncologist.
- 6.3** Treatment machine requirements. Treatment must be given using megavoltage equipment with Cobalt-60, 4-20 MV photons or 5-20 MeV electrons. The minimum Source-Axis Distance (*SAD*) shall be 80 cm.
- 6.4** Treatment techniques. All fields must be treated each day. Treatment volume will include the radiographic abnormality with at least a 2 cm margin. Treatment of the entire bone is not required.
- 6.4.1** Anterior and posterior parallel opposed fields will be used for lumbar spine, sacrum, pelvis (*excluding pubis*), and extremity sites. Equal weighting is recommended, although unequal weighting may be used for the lumbar or sacral spine with a ratio of doses of 1:2 AP:PA. Dose will be prescribed at mid-thickness at the central axis, or at the center of target volume if unequal weighting is used. Alternatives: lumbar spine may be treated with a single PA field, with the dose prescribed to mid-vertebral body as defined by a lateral simulator film. Sacrum may be treated with opposed lateral fields.
- 6.4.2** Single posterior fields will be used for the thoracic spine and scapula, using an *SAD* or *SSD* technique. The treatment depth is set at the middle of the vertebral body, as determined by a lateral simulation film. The scapula may also be treated with opposed oblique (*tangent*) fields
- 6.4.3** The cervical spine may be treated with either parallel opposed lateral fields or with a single posterior field. When lateral fields are used, the isocenter should be at mid-thickness, with the dose prescribed to the mid-vertebral body. For a single posterior field, the dose will be prescribed at a depth of 5 cm or other depth as determined from a lateral simulator film.
- 6.4.4** Pubic bone lesions will be treated with a single anterior field at a depth determined by lateral radiograph or CT scan.
- 6.4.5** Clavicular lesions will be treated with a single anterior field at a depth of 3 cm. The dose will be prescribed to the 3 cm depth. An alternative depth may be used as determined by CT scan or other radiographs.
- 6.4.6** Rib metastases may be treated with electrons or with photons. When electrons are used, the appropriate energy should be chosen such that the entire lesion is covered by the 90% (*or higher*) isodose curve. The dose will be prescribed to the 100% isodose line. When photons are used, parallel opposed fields may be used, with the depth prescribed to the mid thickness. Tangential fields are strongly encouraged to avoid treatment of underlying structures. A single field may be used to cover the lesion, with the depth set at the estimated depth of the rib lesion, and the dose prescribed to that level.
- 6.4.7** When more than one osseous site is to be included into one treatment field, the treating radiation oncologist may use differing field arrangements at her/his discretion, with the fields arranged to provide relatively uniform treatment of the target sites with a minimum of uninvolved normal tissues.
- 6.5** **Treatment Modification Based on Toxicity:** Follow the modifications in the following table.

TOXICITY	AGENT	DOSAGE CHANGE
<i>Based on interval toxicity</i>		
KPS drops to 30 OR Grade 3-4 toxicity	Arm 1 30.0 Gy in 10 fractions	Break of ≤ 1 week; if no improvement drop from study
	Arm 2 8.0 Gy in a single fraction	No modifications

6.6 **Risks of Radiation Treatment**

Expected side effects, depending on the area treated, include nausea, vomiting, diarrhea, skin erythema and alopecia in the irradiated area, esophagitis, myelosuppression, urinary urgency and frequency, and pneumonitis.

6.7 **Radiation Toxicity Reporting (4/30/01)**

- 6.7.1** For acute RT toxicity (*within 90 days from starting RT*) the RTOG Acute Radiation Morbidity Criteria should be used (*Appendix IV*). If the patient develops \geq grade 3 RT-related toxicity, RT should be withheld. Treatment can resume once grade 3 RT-related toxicity is no longer present if it resolves in less than one week; otherwise discontinue treatment.
- 6.7.2** For long-term toxicity (*persisting or beginning beyond 90 days of treatment start*) refer to the RTOG Late Effects Radiation Morbidity Criteria in Appendix IV.

- 6.7.3** Unusual toxicities, and all grade 4-5 toxicities are to be reported by telephone to RTOG Headquarters.
- 6.7.4** A written report containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters. NCCTG members will send this information to the NCCTG Operations office who will forward it to RTOG. See Appendix V.

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

Not applicable to this study.

9.0 ECONOMIC IMPACT OF TREATMENT

- 9.1** Data on resources used during the radiotherapy will be compared by using the information from the completion of Radiation Therapy form. The information collected will include specifics of treatment procedures, including numbers of procedures performed and CPT codes of those procedures.
- 9.2** Information on the medications used by the patient at home will be collected. This will provide information concerning the amount and type of pain medication, as well as new medications related to cancer treatment, used by patients. Specific medications tracked will consist of narcotic analgesics, non-narcotic analgesics (*NSAIDs and acetaminophen*), corticosteroids, neuroleptics and appetite stimulants (*megace, dronabinol*).
- 9.3** Resource use of other treatment involved will be assessed at the same times as the Wisconsin Brief Pain Inventory and the FACT scale. Information to be gathered will consist of hospitalizations (*and reason for admission*), other cancer related treatment, and home health visits.
- 9.4** A detailed cost survey will be collected at selected institutions to estimate the costs model. A cost utility or cost effective analysis will be performed. The costs for each arm will be divided by the quality adjusted time without pain or progression of pain to arrive at the cost utility analysis. Differences in cost will be assessed using univariate tests of means (*analysis of variance for comparisons of both groups and Student t-tests for pairwise comparisons*). Direct medical costs will be initially used in the calculation of costs with an attempt to estimate indirect cost of treatment (*the patients opportunity cost of coming in for daily treatments*). Costs will be calculated from a societal prospective. To assess differences in costs between histology, number of painful sites, treatment sites, worst-pain score, and receiving pamidronate/biphosphanates, a multivariable ordinary least-squares regression will be performed. Analysis of costs will be blinded so the person(s) who analyze costs will not know which treatment arm the patient received.

10.0 PATHOLOGY

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (4/30/01)

Assessments	Pre RX	At 2 weeks	At followup per Section 12.0
History & Physical	X		X
Histologic Confirmation	X		
Physician Prediction of Survival	X		
Pregnancy test (<i>as applicable</i>)	X ^a		
KPS	X	X ^d	X ^d
Pain Score & Narcotic Score	X	X ^d	X ^d
Radiographic Assessment	X ^b		X ^c
FACT-G; Pain Assessment (<i>BPI</i>) ^f	X	X ^d	X ^d
Health Utilities Index	X		X ^e
Toxicity Measurement		X ^d	X ^d

- a. Within 7 days prior to randomization
- b. Within 8 weeks prior to randomization
- c. See Sections 11.2.5 and 11.2.6.
- d. At 2 and 4 weeks, and at 2, 3, 6, 9, 12, 18, 24, 30, 36, 48 and 60 months.
- e. At 3 months and at progression.
- f. BPI must be done pre randomization for eligibility score.

11.2 Response Definitions and Retreatment

- 11.2.1** Response will be determined by follow-up questionnaires and phone call interviews when necessary for completeness in poor compliance patients. Time to maximal pain relief: The time from the first day of irradiation until the lowest pain score for average pain after radiation therapy. The “worst pain score” will be used as the marker for treatment success or failure.
- 11.2.2** Treatment failure. All the following are considered treatment failures:
- 11.2.2.1** A pain score that does not change within 8 weeks from the start of radiation therapy.
 - 11.2.2.2** A 2 point increase in worst pain score that is sustained at a higher level in the month following the first day of radiation therapy.
 - 11.2.2.3** A pain score that drops by at least 2 points and subsequent sustained rise (*on 2 successive questionnaires*) of pain score by at least 2 points.
- 11.2.3** Patients experiencing a decrease of 2 points in the worst pain score for two consecutive analysis periods will be considered to have partial pain relief.
- 11.2.4** Complete pain relief is defined as an average pain score of 0 for two consecutive analysis periods.
- 11.2.5** All patients with a pain score > 4 in the treated area at the 3-month followup will have plain radiographs to assess for bone stability and pathologic fractures.
- 11.2.6** Any patient with progressive pain in the treated area should have plain radiographs of the area to assess for bone stability and pathologic fracture.

11.3 Retreatment

- 11.3.1** Previous studies have shown that pain relief from radiotherapy may take several weeks to become apparent. Therefore, patients should not be re-irradiated to the same treatment site for at least 4 weeks after completion of treatment on this study unless the patient has an increase of 2 points on the worst pain score.
- 11.3.2** Dose and fractionation schemes are left to the discretion of the treating radiation oncologist.

11.4 Quality of Life Assessments

- 11.4.1** The schedule of questionnaires is to be reviewed with the patients before study entry.
- 11.4.2** The follow-up questionnaires will be given to the patients at the end of their planned course of irradiation with the dates of evaluation indicated.
- 11.4.3** Patients who fail to respond to the questionnaire in a timely fashion will receive follow-up phone call interviews as to pain status if there is a lapse of more than 10 days since the due date of the questionnaire.
- 11.4.4** Phone call interviews will be conducted as follows:
- 11.4.4.1** Please read the instructions written on the quality of life questionnaires to the patient. It should take approximately 20 minutes for the patients to fill out the questionnaires. An explanation of specific administration times of the questionnaire should be given to the patient.
 - 11.4.4.2** Patients should be instructed to fill out all questions even if they consider a symptom or concern to be related to something other than the cancer or the therapy.
 - 11.4.4.3** The patient may receive assistance filling out the questionnaire if necessary. It is, however, important to avoid influencing their response. Any assistance along with the reason for assistance must be noted on the cover form. Family members are not permitted to assist the patient filling out the questionnaire. It is preferable that family members are not present while the patient fills out the questionnaire so as not to influence the patient.
 - 11.4.4.4** The questionnaire must be reviewed after the patient completes the form to be sure all items are answered and that each item has only one response circled.
 - 11.4.4.5** It is permissible to send the questionnaire home with the patient in a sealed envelope if he/she is too sick to fill out at the time of their appointment. The questionnaire may be mailed to a patient if they were unable to keep their followup appointment. When questionnaire has been sent home or mailed, patients should be instructed not to open the envelope until they are contacted by phone by the protocol assistant or nurse. Patients should have the questionnaire in front of them while they are asked which response they would choose. The data manager then fills out the form. Again, this assistance and the reason must be documented on the cover sheet.

- 11.4.5 Assessments will be done prior to study treatment and with every followup form through year 5. See Section 11.1.
- 11.4.6 If a patient refuses or is unable to complete a questionnaire at a specified data collection point, the cover form should still be completed. The patient should be asked again at the next data collection point to fill out the questionnaires.

11.5 Quality of Life Instruments

11.5.1 Two instruments will be used in this clinical trial. The first instrument, the Functional Assessment of Cancer Therapy (*FACT-G*),¹⁷ is a 33 item general cancer quality of life measure chosen to assess the multi-dimensional aspects of quality of life previously described. *FACT-G* assesses five conceptual domains. These domains include physical well being, social/family well being, emotional well being, functional well being, and treatment satisfaction. *FACT-G* also includes items that will address components of reactive pain including anxiety, depression and suffering. The second instrument, the Wisconsin Brief Pain Questionnaire,³⁴ better known as the Brief Pain Inventory (*BPI*), will assess sensory and reactive components of pain.

11.5.1.1 *FACT* developed by Cella et al. is a five point Likert patients self rating scale. Respectable validity and reliability have been demonstrated with high correlations with measures such as the Functional Living Index - Cancer (*FLIC*; $r=.79$) and the Brief Profile of Mood States (*POMS*; $r=.65$). The correlation with activity level as measured by the ECOG 5 -point performance status rating was moderately high ($r=.56$). The sensitivity of *FACT* was demonstrated by total scores differentiation among patients according to stage of disease and ECOG performance status rating. Test-retest reliability was high for the five subscales with correlation co-efficients ranging from a high of .88 for physical well being to a low of .82 for social and emotional well-being.¹⁷

11.5.1.2 The Brief Pain Inventory (*BPI*) developed by Daut et al. was modeled after the McGill Pain Questionnaire.^{34,35} The *BPI* is a 17 item patient self rating scale assessing demographic data, use of medications, as well as sensory, and reactive components of pain. Respectable reliability has been demonstrated over short intervals using test retest item correlation; worst pain, $r=.93$; usual pain, $r=.78$; pain now, $r=.59$. Evidence of validity of the *BPI* comes from several sources. The relationship between use of pain medications and overall pain ratings was examined. The percentage of patients taking pain medications increased with high pain ratings. Significance was demonstrated between increased medication use and high pain ratings for both narcotic ($\chi=28.17, df=3, p<0.002$) and non narcotic ($\chi=23.75, df=3, p<0.002$) pain relievers. Validity of the *BPI* was also supported by the moderate correlation between worst pain intensity ratings and ratings of interference with six areas of activity and mood ($r=.245$ to $.478, p<0.02$ for all but social relationships were $p<0.05$). And finally, there is a logical pattern in the differences in inter-correlations among various pain and activity interference measures for different diseases.³⁴

The *BPI* includes items that will address components of sensory pain including severity, location, chronicity and degree of relief due to therapy. The *BPI* also has items that address reactive pain components including depression, suffering and perceived availability of relief.

11.6 Health Utilities Index (*HUI*)

The Health Utilities Index is a generic multiattribute, preference-based system for assessing health status. This system consists of a two-step approach to the measurement of health status: 1) the assessment of health status, defined as functional capacity, the extent to which deficits inhibit normal functioning, independent of the value that subjects attach to that health status, and 2) a multiattribute utility function used to value health status.

The *HUI* was developed consistent with classic utility theory for decision making under conditions of uncertainty as postulated by vonNeumann and Morgenstern (*vonNeumann & Morgenstern, 1994; Luce & vonWinterfeldt, 1994*). It meets the additional assumption of utility independence required for multiattribute outcomes, including additive and multiplicative utility independence. Work is in progress to fit the order - one multicenter model of utility independence to the Mark III, implying there is no interaction (*synergy*) between preferences for any one attribute and the fixed levels for the other attributes.

The *HUI*-Mark III system defines 972,000 health states using five or six functional capacity levels for eight attributes including vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Several versions exist and it is the 17 item, self-administered, English language, adult version that will be utilized in this study.

Acceptable reliability and validity of both the questionnaire and the scoring formula have been established (84-87). Utility scoring functions were derived from a combination of visual analog scale and standard gambles. Utility scores and the formulas for the Mark II system are public domain and are described in Table 1. (*The utility scores and formula for Mark III are provided upon contract with the McMaster Research Group*). The utility is then multiplied by the outcome of interest, usually survival is measured in years, to derive the measure of effectiveness known as quality adjusted life years (*QALY's*).

Table 1. Multiattribute utility function on dead-healthy scale for HUI Mark II system

<u>Sensation</u>		<u>Mobility</u>		<u>Emotion</u>		<u>Cognition</u>		<u>Self-Care</u>		<u>Pain</u>		<u>Fertility</u>	
x ₁	b ₁	x ₂	b ₂	x ₃	b ₃	x ₄	b ₄	x ₅	b ₅	x ₆	b ₆	x ₇	b ₇
1	1.00	1	1.0	1	1.00	1	1.00	1	1.00	1	1.00	1	1.00
2	0.95	2	0.97	2	0.93	2	0.95	2	0.97	2	0.97	2	0.97
3	0.86	3	0.84	3	0.81	3	0.88	3	0.91	3	0.85	3	0.88
4	0.61	4	0.73	4	0.70	4	0.65	4	0.80	4	0.64		n.a.
	n.a.	5	0.58	5	0.53		n.a.	n.a.		5	0.38		n.a.

Formula: $-u^* = 1.06 (b_1 x_1 b_2 x_2 b_3 x_3 b_4 x_4 b_5 x_5 b_6 x_6 b_7) - 0.06$

where u* is the utility of the health state on a utility scale where dead has a utility of 0.00 and healthy has a utility of 1.00. Because the worse possible health state was judged by respondents as worse than death, it has a negative utility of -0.03. The standard error of u* is 0.015 for measurement error and sampling error, and 0.06 if model error is also included. x_l is attribute level code for attribute l; b_l is level score for attribute l. (*Feeney, Torrance & Furlong, 1996, Quality of Life and Pharmacoeconomics in Clinical Trials, Phila: Lippincott-Raven; Permission for use is limited to this study only and has been granted by the developers of the HUI 2/3 [fax 905/546-5211]*)

12.0 DATA COLLECTION

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission (4/30/01)

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Pathology Report (P1)	
FACT-G Questionnaire (FA)	
Brief Pain Inventory (PQ)	
(Pre randomization for eligibility)	
Health Utilities Index (HP)	
Radiotherapy Form (T1)	Within 1 week of RT end
<u>Dosimetry Information:</u>	
PreRx Bone Radiograph (C4)	
Daily Treatment Record (T5)	
Films (simulation and portal) (TP)	
Calculations (TL)	
Follow-up Form (F1)	At 2 and 4 weeks from start of treatment; at 2 and 3 months; then q 3 months x 3; q 6 months x 3 years, then annually. Also at progression/relapse and at death. The QF and PF forms will be collected through year 5 only.
Follow-up FACT-G Questionnaire (QF)	
Follow-up Brief Pain Inventory (PF)	
Health Utilities Index (HP)	At 3 months, and at progression.

Plain Radiographs of Treatment Area (C4)

As applicable for pain score > 4 at 3 months,
or progression of pain at any time

Autopsy Report (D3)

As applicable

12.2 Dosimetry Submission

All dosimetry information will be sent directly to RTOG Headquarters, 1101 Market Street, 14th Floor, Philadelphia, PA 19107 and must be identified with labels available from RTOG. **All items must be identified with both RTOG and NCCTG's study and case numbers. Unidentified films will be returned.**

12.3 Data Forms

RTOG will send a patient-specific forms due calendar and labels and a forms package to RTOG members for each case registered. NCCTG will attach a forms appendix to their members' version. It will be the responsibility of NCCTG members to copy the attached forms and to maintain a supply of available forms for data submission. **The RTOG and NCCTG assigned case and study numbers must be recorded on all data items submitted.** All forms for NCCTG members (*except dosimetry materials*) will be submitted to NCCTG for forwarding to RTOG.

12.4 Request for Study Information and Forms Request:

Requests for additional information or clarification of data will be routed through NCCTG requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response. Periodically (*generally three times a year*), computer-generated lists identifying delinquent material are prepared and are routed through NCCTG for distribution.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 The primary endpoint of this trial is frequency and duration of complete pain relief.

13.1.2 Frequency and duration of complete narcotic relief.

13.1.3 Patient assessed quality of life.

13.1.4 Overall survival from time of randomization.

13.1.5 The frequency of severe (\geq grade 3) toxicities.

13.1.6 The incidence of pathologic fracture.

13.2 Quality of Life Endpoints

13.2.1 *Sensory Pain Relief* - will be assessed by items on the BPI that measure severity, location, chronicity, and degree of relief due to therapy by demographic data that will track use of narcotic and non-narcotic pain medications. Ninety percent of patients should demonstrate some sensory pain relief reported as a decrease in severity rating and use of pain medications and increase in the pain relief rating. The expected change in these indicators should occur at 3 months from the end of radiation therapy on the standard treatment arm. Forty percent of patients should demonstrate complete sensory pain relief by 6 months from the end of radiation therapy as reported by the same indicators. Duration of sensory pain relief should approach a mean of 24 weeks for those patients reporting some relief and 13 weeks for those patients reporting complete relief. For patients who survive one year or more, 60% should report sustained relief on the standard treatment arm.

13.2.2 *Reactive Pain Relief* - Other than Karnofsky Performance Status, there is little information in the literature on which to base estimates of reactive pain relief due to radiation therapy. At 6 months after the end of radiation therapy, it is estimated that 63% of patients on the standard treatment arm should report minimal interference with activities of daily living (ADL) as measured by Karnofsky >60, and selected items addressing ADL's on both FACT-G & the BPI.

13.2.3 The five conceptual domains of physical well being, social/family well being, treatment satisfaction, emotional well being and functional well being will be analyzed using FACT-G. We, however, assume a high correlation between reactive pain relief and the total quality of life score as measured by relief due to radiation therapy and the total quality of life score.

13.3 Sample Size

Pain and narcotic relief are documented by the BPI, Pain Assessment Status and Medication Record and will be assessed at 3 months from the end of radiotherapy. Blitzer¹¹ estimated that complete pain and narcotic relief on the standard arm were 46%. We estimate medical equivalence if at least 36% of the rapid treatment arm patients achieve complete pain and narcotic relief. Using Blackwelder's method for

equivalence trials, 852 analyzable patients will be required.³⁶ Assuming an ineligible or inevaluable (*no data submitted*) rate of 10% then the total sample size required will be 938 patients. This sample size will ensure a 90% ($B=0.10$, type II error) probability of detecting a greater than 21.7% change in complete pain and narcotic relief, while rejecting the null hypothesis at the 95% level ($\alpha=0.05$, *one sided type I error*).

Quality of life will be measured via FACT. A difference of 5.4 in FACT has been shown to be clinically significant. It is anticipated that a large proportion of **the 938 randomized patients** will comply with the completion of these questionnaires. The mean, variance, completion rates for initial and follow-up questionnaires impact the sample size calculation. See Section 13.7 for specific plan of assessment of these parameters during the accrual phase.

The estimated median survival for the standard arm is 6 months, and the rapid treatment arm will be assumed to be medically equivalent if the median survival is 4.9 or more months. Assuming exponential survival, by Rubinstein's method,³¹ then this sample size will ensure the same statistical power and significance level as stated above.

The sample size must provide sufficient evidence of equivalent outcome by treatment arm within single and multiple painful sites. If 50% of the sample are patients with a single painful site then the power will be 66% within each subset. If only 40% of the sample has a single painful site, the power will be 58% within the single painful site subset. If the study sample is comprised of 30% or fewer patients with a single painful site at the time of interim analysis (*Section 13.6.2*) then a revised sample size will be proposed to insure a minimum power of 50% in each subset. There will be sufficient numbers of patients to determine any difference in pathologic fracture rates between the two treatment arms.

13.4 Patient Accrual

The patient accrual is projected to be 31.3 patients per month from the RTOG and 14 patients per month from the NCCTG. This trial should complete the accrual phase within two years. If the accrual is less than 15 patients per month, the study will be re-evaluated concerning feasibility.

13.5 Inclusion of Women and Minorities

In conformance with the National Institute of Health (*NIH*) Revitalization Act of 1993 about inclusion of women and minorities in clinical research, we have also considered the possible interaction between gender/to race and treatments. The participation rates of men and women and the level of minority participation are estimated below:

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female			49	19	204		272
Male			119	48	499		666
Unknown							
Total			168	67	703		938

13.6 Randomization Scheme (4/1/99)

The treatment allocation will be one using a randomized permuted block design. Balance will be maintained within institution. The patients will be stratified by number of painful sites (*solitary vs. multiple*), treatment site (*weight-bearing vs. non weight-bearing*) initial worst pain score (*< 5 [with ≥ 60 mg morphine or equivalent] vs. 5-6 vs. 7-10*) and use of pamidronate/biphosphonates (*yes vs. no*).

13.7 Analysis Plans

13.7.1 Interim analyses of accrual and toxicity data

Interim reports with statistical analyses will be prepared every six months until the initial paper reporting the treatment results has been submitted. The interim reports will contain information about:

- a. the accrual level and estimate of completion;
- b. the distribution of patients with respect to pretreatment characteristics, including participation rates of women and minorities
- c. the frequency and severity of the toxicities.
- d. completion rates of initial and follow-up FACT and BPI scales.

13.7.2 Interim Analyses of Primary Study Endpoints

There will be two interim analyses of the primary study endpoint (*pain and narcotic relief*). The interim analyses will proceed according to the following table.³⁷

TOTAL ACCRUAL	SIGNIFICANT LEVEL
50%	0.00250
100%	0.00296

If any interim analyses exceed the listed significance level, which were calculated to ensure an overall significance level of 0.05, the accrual will be suspended. At the time of these analyses, power calculations will be made for women and minority participation to assess the need for revised accrual estimates. The results of these interim analyses will only be reported, in a blinded fashion, to the RTOG Data Monitoring Committee (DMC). A report with recommendations will be given to the study chair. Any problems or recommendation identified by the DMC, not results, will be reported to the CCOP Committee, which is responsible for this study, and if necessary, to the RTOG Executive Committee, so corrective action can be taken.

13.7.3 Interim Analyses of Pain and QOL scales

There will be one analysis of FACT and BPI scales during the accrual phase. This analysis will be performed after 200 patients (*100 per arm*) have been accrued and followed for 3 months. This analysis will include participation and completion rates for BPI and FACT, treatment arms will be combined to estimate mean and variances for power calculations. The results of this analysis will be presented to the DMC for consideration of the number of patients needed to answer associated study endpoints.

13.7.4 Analysis and Reporting of Initial Treatment Results

The major analysis will be undertaken when each patient has been potentially followed for a minimum of 6 months. The usual components of this analysis are:

- 1) tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;
- 2) reporting institutional accrual;
- 3) distribution of the important prognostic factors by assigned treatment;
- 4) observed results concerning the study endpoints. Analysis of pain and narcotic relief, BPI and FACT will be performed using a stratified Wilcoxon to account for the covariation of Strata. Survival analysis will utilize the Peto-Prentice modified Wilcoxon.

Further subgroup analyses may be conducted (*depending upon the sizes within the subgroups*) for the purpose of identifying patterns of treatment responses. Ineligible/inevaluable patients will be excluded from all analyses. The p-value of 0.04831 will be used, thus correcting for previous interim tests.

- 5) Regression analysis will be performed with respect to study endpoints to determine the importance of pamidronate/biphosphonate use, number of painful sites, treatment site, assigned treatment, initial pain score, performance status, and other potential prognostic factors predicting outcome.

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APPENDIX I

RTOG 97-14

RANDOMIZED TRIAL OF PALLIATIVE RADIATION THERAPY FOR OSSEOUS METASTASES: A STUDY OF PALLIATION OF SYMPTOMS AND QUALITY OF LIFE

Sample Patient Consent Form

RESEARCH STUDY

I am being asked to participate in this radiation therapy study for bone pain. I have the opportunity to decide whether to undergo the procedure after knowing the risks, benefits, and alternatives. This study will help determine if a single treatment is as effective as the usual 10 treatment schedule.

PURPOSE OF THE STUDY

It has been explained to me that I have a tumor that has spread to my bones, which is causing pain. Radiation therapy is a frequently used treatment for this type of problem. Previous studies have shown that radiation therapy is a good form of treatment to reduce or relieve this type of pain for most patients. This study is to see whether one large dose of radiation therapy, when compared to 10 smaller doses, will give complete pain relief. "Gray" is the term used to measure the dose of radiation that is given. This study will also see how each treatment affects the quality of my life. It will also determine the difference in costs between the two treatment schedules.

Sometimes when tumor spreads to the bone, it causes the bone to get weak. It may even break (*fracture*). Radiation therapy is usually effective in preventing my bones from breaking. This study will also see if one radiation treatment is as effective as 10 radiation treatments in preventing fractures.

DESCRIPTION OF PROCEDURES

This study involves at random (*by chance*) assignment to one of two treatment arms. It is not clear right now which of the two is better. For this reason, the therapy that is to be offered to me will be based upon a the method of selection called randomization. Randomization means that my physician will call a statistical office that will assign me one of the two treatments by computer. The chance of my receiving one of the two therapies is approximately equal. I will be assigned to one of two treatments:

Treatment 1: I will receive radiation treatment to the painful area once a day. I will have five treatments a week for two weeks. The amount of radiation given each day is 3 Gray. The total amount of radiation will be 30 Gray.

Treatment 2: I will receive one treatment with radiation. The total dose will be 8 Gray.

Before, during and following the treatment, I will be asked to complete questionnaires regarding my pain and pain relief. The questionnaires also ask questions to find how much the treatment affects my quality of life, and how the treatment affects other aspects of my life, such as time lost from work. It takes approximately 15-20 minutes to complete these questionnaires. I will be asked to complete them before I start treatment and each time I see my doctor. Some of the questions regarding quality of life are of a personal nature, and may be upsetting to some patients. My doctor and nurse will be available to discuss these questions if I have a concern or problem.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Possible side effects of the radiation therapy are hair loss in the area treated, dryness or irritation of skin in the area being treated (*like a sunburn or tanning*), and temporary tiredness. When certain areas of the body are treated, nausea, vomiting and sore throat, may occur. My blood counts may also be lowered causing tiredness or easy bruising. If my abdominal area is treated, I may have diarrhea, or feel as if my bladder is too full (*urgency*) causing me to urinate often. I can check with my doctor or nurse for more information on the side effects of my treatment.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood and urine tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. The use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

This treatment will not be offered to female patients who are pregnant. If I am a sexually active women of child-bearing potential I must take precautions to avoid pregnancy. It is not known how this treatment could affect an unborn child. I will need to have a negative pregnancy test before entering this study. I will notify my doctor immediately if I become pregnant.

CONTACT PERSONS

If injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide. I will receive no other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. _____ the investigator
_____. In addition, I may contact _____
_____ at _____
for information regarding patients' rights in research studies.

BENEFITS

It is not possible to predict whether any personal benefit will result from the treatment program. A possible benefit would be complete pain relief. The information learned from this study may be used scientifically and may possibly be helpful to others. A potential benefit of the one dose treatment is less travel time.

Should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

Alternatives that could be considered in my case include radiation therapy without being on this study either alone or with chemotherapy or treatments to make me feel better. For some tumors, hormone treatments may be used as well. An additional alternative is no further therapy, which would probably result in continued pain and growth of my tumor. My doctor can provide me with detailed information about my disease and the benefits of the various treatments available. I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain procedures used in this protocol. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw from this study at any time without prejudice to my subsequent care. I am free to seek care from a physician of my

choice at any time. If I do not take part in or withdraw from this study, I will continue to receive care. In if there is a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

Records of my progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*) . The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), and other groups or organizations that have a role in the conduct of this study may have access to medical records that contain my identity. No information by which I can be identified by name will be released or published.

I have read all the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (*or Legal Representative*)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX III

PAIN AND NARCOTIC CATEGORIES AND SCORES

<u>PAIN</u>		<u>ANALGESIA</u>	
S E V E R E I T Y	0 - No pain	0 - None	
	1 - Mild	1 - Analgesics (<i>ASA, Bufferin, Tylenol, Anacin, etc.</i>)	
	2 - Moderate	2 - Mild Narcotic, (<i>< 1/2 gr. codeine, Darvon, etc.</i>)	
	3 - Severe	3 - Moderate Narcotic (<i>> 1/2 < gr. codeine, Percoan, etc.</i>)	
		4 - Strong Narcotic, (<i>> 1gr. codeine, demerol, morphine, etc.</i>)	
F R E Q U E N C Y	0 - None	None	
	1 - Occasional (<i>< daily</i>)	1 - p.r.n. (<i>< daily</i>)	
	2 - Intermittent (<i>at least daily</i>)	2 - q.d. (<i>1 tab. or cap./day</i>)	
	3 - Frequent (<i>> 1 < 3 daily</i>)	3 - b.i.d. t.i.d. (<i>> 1 < 4 tab. or cap./day</i>)	
	4 - Constant (<i>most of the time</i>)	4 - > t.i.d. (<i>> 4 tab. or cap./day</i>)	

Pain Score = Pain Severity Grade x Pain Frequency Grade

Narcotic Score = Analgesia Severity Grade x Analgesic Frequency Grade

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone .
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction that is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (*IDB*)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent.

Report **by phone** within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days.

- All deaths within 30 days of termination of the agent. As above
- All life threatening (*grade 4*) events that may be due to agent. As above
- First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters.
**A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours
**A written report must be sent to RTOG within 10 working days with a copy to IDB.
(*Grade 4 myelosuppression not reported to IDB*)
- All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**.
**A written report to follow within 10 working days.
- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. **Report **in writing** to RTOG Headquarters and IDB within 10 working days.

** See attached (*if applicable to this study*) NCI Adverse Drug Reaction Reporting Form

APPENDIX VI (4/30/01)
Analgesic Conversion Tables

<u>EQUIANALGESIC POTENCY CONVERSION</u>		
<u>Name</u>	<u>Equianalgesic Dose (mg) po</u>	
Morphine	60	
Hydromorphone (<i>Dilaudid</i>)	7.5	
Methadone (<i>Dolophine</i>)	20	
Oxycodone	30	
Levorphanol (<i>Levo-Dromoran</i>)	4	
Codeine	200	
Vicodin	60	
<u>TRANSDERMAL FENTANYL (DURAGESIC) DOSE PRESCRIPTION BASED UPON DAILY MORPHINE EQUIVALENCE</u>		
<u>Oral 24-hour morphine (mg/day)</u>	<u>Duragesic Dose (ug/h)</u>	
45-134	25	
135-224	50	
225-314	75	
315-404	100	
405-494	125	
495-584	150	
585-674	175	
675-764	200	
765-854	225	
855-944	250	
945-1034	275	
1035-1124	300	
<u>NARCOTIC EQUIVALENCY INDEX</u>		
<u>NARCOTIC</u>	<u>ROUTE</u>	<u>CONVERSION FACTOR</u>
Morphine	IM/IV	1.00
	po	0.17 for single dose trial; 0.33 for chronic administration
Hydromorphone (<i>Dilaudid</i>)	IM	6.67
	po	1.33
Codeine	IM	0.08
	po	0.05
Oxycodone*	IM	0.67
	po	0.33
Levorphanol (<i>Levodromoran</i>)	IM	6.25
	po	3.13
Meperidine (<i>Demerol</i>)	IM	0.10
	po	0.03
Methadone (<i>Dolophine</i>)	IM	1.38
	po	0.69
* 1 tablet of Tylox, Percocet, or Percodan contains 5 mg of oxycodone.		