Radiotherapy in bone metastasis : the Dutch bone metastasis study

Linden, Y.M. van der

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Cost-utility analysis of single versus multiple fraction radiotherapy in patients with painful bone metastases

Wilbert B. van den Hout, Yvette M. van der Linden, Elsbeth Steenland, Ruud G.J. Wiggenraad, Job Kievit, Hanneke de Haes, Jan Willem H. Leer for the Dutch Bone Metastasis Group

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Abstract

Background : Radiotherapy is an effective palliative treatment for cancer patients with painful bone metastases. Although single and multiple fraction radiotherapy are thought to provide equal palliation, which treatment schedule provides better value for the money is unknown. We compared quality-adjusted life expectancy (the overall valuation of the health of the patients) and societal costs for patients receiving either single or multiple fraction radiotherapy.

Methods : A societal cost-utility analysis was performed on a Dutch randomized, controlled trial of 1157 patients with painful bone metastases that compared pain responses and quality of life from a single fraction treatment schedule of 8 Gy with the treatment schedule of six fractions of 4 Gy each. The societal values of life expectancies were assessed with the EuroQol classification system (EQ-5D) questionnaire. A subset of 166 patients also answered additional questionnaires to estimate nonradiotherapy and nonmedical costs. Statistical tests were two-sided.

Results : Comparing the single and multiple fraction radiotherapy schedules, no differences were found in life expectancy (43.0 versus 40.4 weeks, $p= 0.20$) or quality adjusted life expectancy (17.7 versus 16.0 weeks, $p= 0.21$). The estimated cost of radiotherapy, including retreatments and non-medical costs, was statistically significantly lower for the single fraction schedule than for the multiple fraction schedule ($ 2438 versus $ 3311, difference= $ 873, 95% confidence interval (CI) on the difference $ 449 to $ 1297, $p< 0.001$). The estimated difference in total societal costs was larger, also in favor of the single fraction schedule, but it was not statistically significant ($ 4700 versus $ 6453, difference= $ 1753, 95% CI on the difference= -$ 99 to $ 3604, $p= 0.06$).
For willingness-to-pay between $ 5000 and $ 40000 per quality adjusted life year the single fraction schedule was statistically significantly more cost effective than the multiple fraction schedule ($p\leq 0.05$).

Conclusions : Compared with multiple fraction radiotherapy, single fraction radiotherapy provides equal palliation and quality of life, and has lower medical and societal costs, at least in the Netherlands. Therefore, single fraction radiotherapy should be considered as the palliative treatment of choice for cancer patients with painful bone metastases.

Introduction

Radiotherapy is an effective and well-accepted palliative treatment modality for cancer patients with painful bone metastases. Treatment is generally given in an outpatient setting with patients visiting the clinic daily during their treatment period. Different treatment schedules can be used, ranging from a single fraction to more protracted regimens, consisting of multiple fractions and stretching over several weeks. Although there is still some debate over the optimal treatment schedule,[1,2] single fraction[3-9] and short term radiotherapy[10-12] have been shown to be as effective as long term treatments in reducing pain.

The 1996 Dutch Bone Metastasis Study was a large randomized trial in which patients with painful bone metastases received palliative radiotherapy either in a single fraction of 8 Gy or in 6 fractions of 4 Gy each.[9] At the conclusion of the study, no statistically significant differences were found in pain response, treatment side effects, and descriptive quality of life. A limited analysis of the costs of radiotherapy suggested that the cost difference was small. The medical costs for the single fraction schedule were only 25% lower, because a large proportion of the costs did not change with the number of fractions. Moreover, the cost difference was decreased by the number of retreatments, which was 25% after the single fraction schedule compared with only 7% after the multiple fraction schedule.[9]

To determine from a societal perspective which radiotherapy schedule provides better value for the money, we performed a full cost-utility analysis of the Dutch Bone Metastasis Study. In the cost-utility analysis, effectiveness is measured by quality adjusted life expectancy, i.e., the overall valuation of the health of the patients in the study. The difference in this quality adjusted life expectancy was compared with the difference in the total costs to society, including the medical costs of radiotherapy, other costs of health care utilization, and costs incurred by the patients.

Material and Methods

Study population

Detail of the patient population and study design for the Dutch Bone Metastasis Study have been published elsewhere.[9] In brief, from March 1996 through September 1998, patients with painful bone metastases from solid tumors were randomly assigned to receive either a single fraction of 8 Gy (n= 579) or 6 fractions of 4 Gy (n= 578). The patients were enrolled in the study from 17 from 21 Dutch radiotherapy institutions. Of the 1157 patients, 36% had bone metastases that were located in the pelvis, 30% in the spine, 10% in the femur, 8% in the ribs, 6% in the humerus, and 10% in other sites. Thirty-nine percent of the patients had breast cancer, 25% had lung cancer, 23% had prostate cancer, and 13% had cancer at other primary sites. Patient age ranged from 32 to 89 years, and 54% of the patients were male.

To be eligible for the study, patients had to have a maximum pain score during the preceding week of at least 2 on an 11-point scale from 0 (no pain) to 10 (worst imaginable pain).[13] The bone metastases had to be confined to an area that could be encompassed in a single radiation treatment field. Patients were excluded from the study if their metastases had already been irradiated, if they had metastases of the cervical spine, or if they had a pathological fracture or compression of the spinal cord. Patients were also excluded if they had renal cell carcinoma or malignant melanoma, because these diseases were expected to respond differently to radiotherapy.

In the study, we aimed to enroll 1200 patients, which would be sufficient to provide the required sample size of 900 assessable patients to demonstrate a 10% difference in the main outcome measure, which was pain response (α= 0.05, ß= 0.15). The Medical Ethics Committees of all participating institutions approved the study and, all patients signed informed consent forms.

Assessment of quality adjusted life years

The patients were followed for up to 2 years after randomization. During this follow-up period, patients completed 13 weekly and 23 monthly questionnaires containing questions on pain at the treatment site, analgesic consumption, treatment side effects, and quality of life. Patients also described their health state using the EuroQol classification system (EQ-5D).[14] The EQ-5D has five attributes (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with three levels each (no problem, some problems, or major problems). The descriptions were transformed into the corresponding EQ-5D utility.[15] This utility reflects the valuation by the general public of the health states provided by the patients, ranging from 1.00 (optimal health), through 0.00 (equivalent to death) to -0.594 (worse than death).

The Dutch Bone Metastasis Study ended in December 1998. At that time, the survival status of all patients was recorded by the data managers of the participating institutions. For the patients who died during the study period, the duration of survival was observed directly. For the surviving patients, the observed survival duration was censured at between 3 and 27 months. Because the patients with censured survival data were likely to have favorable prognosis, neglecting the censured data could bias the analysis by underestimating survival. Therefore, each observed censured survival was increased by the remaining lifetime estimated from the last available EQ-5D utility measurement: extrapolated remaining lifetime in days=156 + 150 x last EQ-5D utility. This formula was estimate from the available survival data by using standard linear regression (R^2 = 0.12). Depending on the value of the last EQ-5D utility, the estimated remaining lifetime ranged from 67 to 306 days.

Shortly before their death, patients tended to stop returning their questionnaires. Because the values of these missing measurements were likely to be worse than the available measurements, neglecting the missing EQ-5D data or carrying forward the last measurement could bias the analysis by overestimating the utilities. Therefore, the values of the missing EQ-5D utilities were estimated from the last available measurement: extrapolated EQ-5D utility = constant x (1 + 98 / remaining lifetime in days) $^{-1}$, with the constant individually fitted to the last available EQ-5D utility. This formula was estimated from the available EQ-5D data using standard linear regression (R^2 = 0.15).

For each patient, quality adjusted life years (QALYs) were calculated from the survival and the EQ-5D utility measurements. Survival was truncated to the maximum follow-up of 2 years. QALYs were truncated to 12 weeks and to 2 years after randomization and were discounted at 3%.

Assessment of costs

For both randomization groups, we estimated the societal costs during the first 12 weeks after randomization. These costs included the medical costs of radiotherapy, the non-medical costs of radiotherapy such as travel costs, medical non-radiotherapy costs such as the costs of hospitalization, and health-related non-medical costs such as the costs of domestic help. Costs were estimated in strict accordance to current guidelines for cost-effectiveness analyses.[16]

The medical costs of the radiotherapy have been reported earlier,[9] but are reported here in greater detail. These costs were estimated for three of 21 Dutch radiotherapy institutions: one of seven academic hospitals, one of eight general hospitals, and one of six independent radiotherapy institutions. The results from the three institutions were weighted relative to the number of each type of institution and combined to generate a typical Dutch radiotherapy department. For each institution, the costs of different types of staff, equipment, material, housing, and overhead were obtained from 1997 annual reports. To estimate the costs of different radiotherapy schedules, each cost item was assigned to one of three allocation bases: treatments, for cost items independent of the treatment schedule: sessions, for cost items proportional to the number of fractions in a treatment schedule: or gray, for cost items proportional to the radiation dose delivered. The annual costs assigned to each allocation base were divided by the annual number of each allocation base to provide an estimate of the unit costs per treatment, per fraction, and per gray. The costs of a treatment schedule consisting of a single fraction of 8 Gy were then estimated as the costs per treatment plus the costs per session plus eight times the costs per gray. Similarly, the costs of a treatment schedule consisting of six fractions of 4 Gy were estimated as the costs per treatment plus six times the costs per session plus 24 times the costs per gray.

The non-medical costs of radiotherapy and non-radiotherapy costs were mostly estimated from cost questionnaires. For practical reasons and to limit the burden to the patients, these questionnaires were filled out by a subsample of the patients over a period of 12 weeks after randomization. Patients from the three institutions from which the typical Dutch radiotherapy department was constructed were asked to fill out six additional bi-weekly cost questionnaires. They could refuse to fill out these additional questionnaires without being excluded from the study. Of 213 consecutive patients enrolled in the trial, 166 (78%) consented to participate. The costs estimated from the cost questionnaires included non-medical costs of radiotherapy (means of transportation, time spent in transit to and from the radiation department, and out-of-pocket expenses), retreatment costs, hospitalization costs, consultation costs (visits to general practitioners, specialist consultations, paramedics, and alternative treatments), purchased medications, in-home nursing care costs, out-of-pocket expenses, costs of domestic help, and paid and unpaid labor costs. From the trial registration, we obtained the schedules of the initial radiotherapy and of retreatments more than 12 weeks after randomization (deduced from the number of treatment days), data on systemic therapy, and the travel distance from the patient's home to the radiation department.

Most cost prices were obtained from Dutch standard prices that were designed to reflect societal costs and to standardize economic analyses.[17,18] Out-of-pocket expenses (e.g., an anti-decubitus bed) were valued as reported by the patients. Transportation costs were valued at $ 0.29 per kilometer for car rides, at $ 2.26 plus $ 1.49 per kilometer for taxi rides, at $ 385 for ambulance rides, and at no costs for walking.[17] Patients' time was valued at minimum wage ($ 8.43 per hour). Hospitalization costs were valued at $ 482 per day for clinical admission, $ 193 per day for outpatient care, and $ 144 per day for nursing home care.[17] The cost of a general practitioner was valued at $ 18 per in-house consultation,[17] $ 9 per telephone consultation, and $ 36 per home consultation. The cost of a specialist was, on average, valued at $ 48 per consultation,[17] with different specialties ranging from $ 25 to $ 86 per consultation. The costs of physiotherapists and other paramedics were valued at $ 19 per consultation,[17] and alternative medicine was, on average, valued at $ 29 per consultation. The cost of purchased medication was valued according to the Pharmacotherapeutic Compass,[18] plus $ 6 per non-drugstore purchase.[17] The costs of in-home nursing care and domestic help were valued at $ 34 and $ 19 per hour, respectively.[17] The reported amount of time spent on paid and unpaid labor was valued at minimum wage, and counted as profits (i.e., negative costs).

Because the type of systemic therapy was not available, the costs of systemic therapy or hormonal therapy were based on Dutch treatment guidelines, with prices obtained from the Pharmacotherapeutic Compass.[18] Breast cancer patients for whom systemic therapy lasted less than 4 months were assumed to have had a CMF regimen valued at $ 2450 (six cycles of cyclofosfamide at 100 mg/m^2 on day 1-14, two cycles of methotrexate at 40 mg/m^2 on days 1 and 8, and two cycles of 5-fluorouracil at 600 mg/m^2 on days 1 and 8). Breast cancer patients receiving longer systemic therapy were assumed to have had hormonal therapy valued at $ 18 per month (tamoxifen 20 mg per day). Prostate cancer patients receiving systemic therapy were assumed to have had hormonal therapy valued at $ 171 per month (either cyproteron at 200 mg per day or goserelin at 3.6 mg subcutaneously per month). In the absence of a reasonable standard therapy, no costs were considered for the remaining patients receiving systemic therapy (8% of all patients).

For each patient who consented to fill out the cost questionnaires, the societal costs during the first 12 weeks after randomization were estimated. For missing cost measurements, the last available measurement was carried forward. Costs are reported at the 2002 price level and were discounted at 3%. Prices were converted to U.S. dollars by using the exchange rate of June 26, 2002 (€1 = $ 0.99).

Cost-utility analysis

In the cost-utility analysis, the 2-year QALYs were compared with the 12-week societal costs. This different time periods were chosen mainly because of the different measurement periods for utilities and costs and was justified by the observation that no statistically significant differences were observed in the costs of radiotherapy after 12 weeks or in the non-radiotherapy costs. Extrapolating costs to a longer time horizon would require substantial modeling assumptions, which could introduce modeling errors. Therefore, the 12-week time period was considered more appropriate for the costs in the cost-utility analysis. Whether a treatment is cost-effective depends on the willingness-to-pay per QALY. Acceptability curves graph the P-value of the hypothesis of equal net benefit (i.e., willingness-to-pay x QALYs − costs) in both randomization groups as a function of the willingness-to-pay.[19,20] Better cost-effectiveness of the schedule with the more favorable net benefit is demonstrated if the difference in net benefit is statistically significant ($P \leq 0.05$). By considering the net benefit, acceptability curves eliminate the problems associated with negative cost-effectiveness ratios. For the acceptability curves, the mean and variance of the QALYs were obtained from the entire sample (n = 1157), and the mean and variance of the costs and their covariance with the QALYs were

LE 1 CHARACTERISTICS AT BASELINE OF THE ENTIRE SAMPLE OF PATIENTS ENROLLED IN THE DUTCH BONE METASTASIS STUDY AND RANDOMLY ASSIGNED TO RECEIVE EITHER SINGLE OR MULTIPLE FRACTION RADIOTHERAPY AND OF THE SUBSAMPLE OF PATIENTS WHO FILLED OUT COST QUESTIONNAIRES*

	Entire sample		Subsample of patients who fi lled out the cost questionnaires	
	8 Gy x 1 (n=579)	4 Gy x 6 (n=578)	8 Gy x 1 (n=80)	4 Gy x 6 (n=86)
, y				
age	65	65	64	66
e	33-89	32-89	36-84	36-86
der, % (n)				
e	53% (307)	55% (317)	49% (39)	65% (56)
ale	47% (272)	45% (261)	51% (41)	35% (30)
al pain score †				
age	6.3	6.3	6.9	7.0
e	2-10	2-10	2-10	2-10
nofsky score ‡				
age	71	72	73	72
e	20-100	20-100	30-100	30-100
nary tumor, % (n)				
nma	40% (233)	38% (218)	42% (34)	28% (24)
	25% (140)	25% (147)	29% (23)	26% (22)
tate	22% (129)	24% (138)	21% (17)	28% (24)
r	13% (77)	13% (75)	8% (6)	19% (16)

Single fraction therapy consisted of a single fraction of 8 gray (Gy). Multiple fraction therapy consisted of six fractions of 4 Gy e subsample of patients who fi lled out cost questionnaires was selected from consecutively enrolled patients in three institutions

Initial pain score= maximum pain score during the week preceding randomization, on an 11-point scale from 0 (no pain) to 10 vorst imaginable pain)

Karnofsky score= Karnnofsky Performance Status Scale, ranging from 100% (normal: no complaints: no evidence of disease) through 70% ares for self: unable to carry on normal activity or do active work) to 0% (death)

obtained from the patients who fi lled out the cost questionnaires (n = 166). The baseline cost–utility analysis used the societal perspective, including all costs incurred during the fi rst 12 weeks after randomization. In addition, we performed sensitivity analyses from the medical perspective (including only medical costs of radiotherapy and of other health care during the fi rst 12 weeks after randomization) and the long-term radiotherapy perspective (including only medical and nonmedical costs of radiotherapy during the fi rst 2 years after randomization).

Statistical analysis

All analyses were performed on an intent-to-treat basis. Groups were compared by use of standard two-sided unequal-variance *t* tests at a 5% signifi cance level,[21] with the corresponding 95% confi dence intervals (CIs) for the difference in means. Reported CIs for means within groups are standard 95% CIs (average ± [$t_{n,0.05}$ x $n^{-1/2}$] x standard deviation). A standard multivariate regression analysis adjusted for the randomization schedule was used to identify statis tically signifi cant predictors of costs among the variables that differed between samples or randomization groups. All statistical analyses were performed with SPSS software (version 10.0; SPSS Inc., Chicago, IL).

Results

The purpose of the study was to determine from a societal perspective which radiotherapy schedule provided better value for the money. The baseline characteristics of the entire sample of 1157 patients enrolled in the study are shown in Table 1, together with the subsample of 166 patients who fi lled out the additional cost questionnaires. The patients in the subsample had worse initial pain scores than the patients in the entire sample (7.0 versus 6.3, P< 0.001). Within the subsample, the group of patients randomly assigned to receive the single fraction treatment schedule included more women (P = 0.03). All other differences were not statistically signifi cant (P > 0.05).

Quality adjusted life years

During the study period, 74% of all patients died. Estimated cumulative mortality for the fi rst 2 years was approximately 88% for both treatment schedules *(Fig. 1)* . The survival curves decreased with an almost constant rate. Of all possible lifetime EQ-5D measurements, 73% were obtained. We assessed the average valuation of health obtained from the EQ-5D measurements among those patients who were still alive at particular weeks since randomization *(Fig. 1)*. The EQ-5D utility improved during the initial months after randomization but appeared to stabilize after approximately 26 weeks. On average, health was valued at approximately 0.40 on a scale from 0.00 (equivalent to death) to 1.00 (optimal health).

FIGURE 1

Proportion surviving and average EuroQol classifi cation system (EQ-5D) utility for the single and multiple fraction radiotherapy groups. Censured survival times and missing EQ-5D utility measurements were extrapolated from the last available EQ-5D utility measurement. EQ-5D utility represents the valuation of health on a scale from 0.00 (equivalent to death) to 1.00 (optimal health). Single fraction therapy refers to a single fraction of 8 Gy. Multiple fraction therapy refers to six fractions of 4 Gy. Weeks since randomization refers to the time the patients were enrolled in the Dutch Bone Metastasis Study.

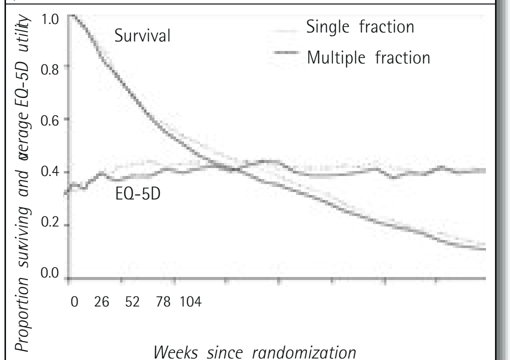
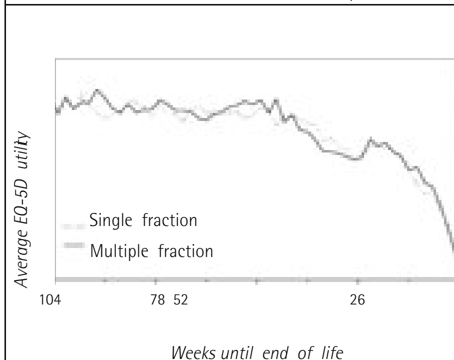


FIGURE 2

Average EuroQol classifi cation system (EQ-5D) utility for single and multiple fraction radiotherapy groups, as a fu of remaining lifetime. Averages are over all measurement particular months, without extrapolation of missing measurements. EQ-5D utility represents the valuation of on a scale from 0.00 (equivalent to death) to 1.00 (opti health). Single fraction therapy refers to a single fraction Multiple fraction therapy refers to six fractions of 4 Gy. until end of life refers to the time until death for patien enrolled in the Dutch Bone Metastasis Study.



We also assessed the average EQ-5D utility as a function of the remaining lifetime, rather than a function of the time since randomization *(Fig. 2)*. Toward the end of life, the valuation of health markedly decreased, to an average valuation of approximately 0.00 (equivalent to death). Sixteen percent of all utility measurements were negative, indicating health states valued as worse than death.

Life expectancy and quality-adjusted life expectancy were slightly more favorable in the single fraction group, but both the short-term and the long-term differences were not statistically signifi cant *(Table 2)*. The overall average life expectancy was approximately 9 months (difference = −2.6 weeks, 95% CI = −6.6 to 1.4 weeks). During the fi rst 12 weeks after randomization, health was valued at approximately one-third the value of optimal health (difference in QALYs during the fi rst 12 weeks = −0.1 weeks, 95% CI = −0.6 to 0.3 weeks). The overall average quality-adjusted life expectancy was approximately 4 months (difference= −1.7 weeks, 95% CI = −4.5 to 1.0 weeks).

TABLE 2 LIFE EXPECTANCY AND QUALITY-ADJUSTED LIFE EXPECTANCY OF THE PATIENTS ENROLLED IN THE DUTCH BONE METASTASIS STUDY AND RANDOMLY ASSIGNED TO RECEIVE EITHER SINGLE OR MULTIPLE FRACTION RADIOTHERAPY*

	Single fraction (8 Gy x 1; n=579) No. of weeks† (95% CI)	Multiple fraction (4 Gy x 6; n=578) No. of weeks (95% CI)	*p*-value
Life expectancy	43.0 (40.1 to 45.9)	40.4 (37.6 to 43.2)	0.20
QALY ≤ 12 weeks‡	4.0 (3.7 to 4.3)	3.9 (3.6 to 4.2)	0.47
QALY's	17.7 (15.7 to 19.7)	16.0 (14.1 to 17.9)	0.21

* *Gy= gray; QALYs= quality-adjusted-life-years; CI= confi dence interval= average ± $t_{n/2,s}$(ε) x standard deviation; P values derived from standard two-sided unequal-variance t tests*

† *Average number of weeks*

‡ *Duration truncated at 12 weeks after randomization to quantify the valuation of short-term quality of life*

TABLE 3 ESTIMATED MEDICAL COSTS OF RADIOTHERAPY FOR THE CONSTRUCTED TYPICAL RADIOTHERAPY DEPARTMENT

		Costs per allocation base (in k$)*		
	Total costs (in k$)	Treatments	Fractions	Gray
Personnel	1977	1240 (63%)	671 (34%)	66 (3%)
Equipment	1217	409 (34%)	429 (35%)	379 (31%)
Material	157	79 (50%)	64 (41%)	14 (9%)
Housing	1489	455 (31%)	1022 (68%)	12 (1%)
Overhead	551	339 (62%)	194 (35%)	19 (4%)
Annual costs (in k$)	5391	2522 (47%)	2379 (44%)	490 (9%)
Annual number		1503	24640	61600
Unit costs (in $)†		1678	96.55	7.95
8 Gy x 1 schedule‡	$ 1838	1678 (1x)	96.55 (1x)	63.60 (8x)
4 Gy x 6 schedule	$ 2448	1678 (1x)	579.30 (6x)	190.80 (24x)

* *One k$ equals $1000. Separate cost items are allocated to treatments if they are independent of the treatment schedule, to sessions if they are proportional to the number of fractions in a treatment schedule, and to gray if they are proportional to the radiation dose delivered*

† *Obtained by dividing the annual costs by the annual number, for each allocation base*

‡ *Obtained by multiplying the unit costs with the number of units of the schedule*

Costs of radiotherapy

We estimated the medical costs of radiotherapy for the constructed typical radiotherapy department *(Table 3)*. The total annual costs for this typical department were 5.391 million dollars. It used a total of 48 full-time equivalent personnel, including 6.7 full-time equivalent radiation oncologists. Approximately two-thirds of the costs of personnel were attributed to the treatments (mainly radiation oncologists and planning) and approximately one-third to the sessions (radiation therapists and technologists). The typical department had 2.3 linear accelerators. The costs of equipment were approximately equally distributed over the three allocation bases: treatments (simulation, planning, and maintenance), sessions (because linear accelerators wear out by turning them on and off), and gray (because linear accelerators wear out according to the duration of the on-period). Costs of housing were primarily assigned to the sessions (i.e., for patient waiting rooms and the linear accelerators), but also to the treatments (i.e., for staff). Costs of overhead were primarily assigned to the treatments and, therefore, do not contribute to the difference in costs between both schedules. The estimated medical costs per allocation base were $ 1678 per treatment, $ 96.55 per session, and $ 7.95 per gray. After multiplying by the appropriate numbers for each radiotherapy schedule, the estimated medical costs were $ 1838 for the single fraction schedule and $ 2448 for the multiple fraction schedule. The estimated difference in medical costs for the initial radiation treatment was therefore $ 610.

We next estimated the total radiotherapy costs *(Fig. 3 and Table 4)*, including retreatment and nonmedical costs during the fi rst 12 weeks after randomization. The largest cost difference was observed in the second 2-week period. At that time, most single fraction treatment schedules had ended, whereas the multiple fraction schedule still generated costs because of the longer waiting time required to schedule the treatment and the longer treatment time. After 7 weeks, the cost difference between the single and multiple fraction groups was reversed because the number of retreatments in the single fraction group was larger than in the multiple fraction group (18% versus 5%, during the fi rst 12 weeks after randomization). This difference in the number of retreatments reduced the initial cost difference by $ 307. Of the nonmedical costs, 64% were associated with travel expenses, 35% were associated with time costs, and 1% were associated with out-of-pocket expenses, such as meals. Because of the difference in the number of radiotherapy fractions in the treatment schedules, the nonmedical costs for the single fraction group were $ 570 less than those for the multiple fraction group. The estimated societal costs of radiotherapy during the fi rst 12 weeks after randomization were $ 2438 for the single fraction schedule and $ 3311 for the multiple fraction schedule, an estimated difference of $ 873 (95% CI = $ 449 to $ 1297).

Although the baseline analysis only included costs during the initial 12 weeks after randomization, we also estimated the costs of long-term retreatments. Among the patients who returned the cost questionnaires, fi ve patients (6%) were retreated after more than 12 weeks in both randomization groups. Including time and travel, the costs of these long-term retreatments were $ 182 in the single fraction group and $ 137 in the multiple fraction group, which was not a statistically signifi cant difference (P = 0.67). The combined short- and long-term retreatment rates in the subset of patients who returned the cost questionnaires (23% for the single fraction group and 11% for the multiple fraction group) were not statistically signifi cantly different (P= 0.18) from those in the entire sample (25% and 7%, respectively).

Societal costs

Of all possible lifetime cost questionnaires, 78% were obtained and used to estimate health care utilization and costs *(Table 4)*. The medical costs (excluding radiotherapy treatment costs) consisted mainly of the costs associated with hospitalizations. They were equivalent in size to radiotherapy treatment costs, but the difference between the randomization groups was not statistically signifi cant (P = 0.18). The total nonmedical costs other than for radiotherapy were small because the additional costs were compensated by the value of the provided labor. Although some of the differences in these nonradiotherapy cost items were considerable, they were all not statistically signifi cant (P= 0.19). The overall medical costs (including the medical costs of radiotherapy and all other medical costs) were estimated to be $ 1344 lower for patients in the single fraction group than for patients in the multiple fraction group (95% CI = −$ 214 to $ 2904). Similarly, the overall societal costs, including all medical and all nonmedical costs, were estimated to be $ 1753 lower for patients in the single fraction group (95% CI = −$ 99 to $ 3604). However, both overall differences were not statistically signifi cant (P = 0.09 and P = 0.06, respectively).

TABLE 4 ESTIMATED HEALTH CARE UTILIZATION AND COSTS PER PATIENT DURING THE FIRST 12 WEEKS AFTER RANDOMIZATION FOR THE SINGLE- AND MULTIPLE-FRACTION RADIOTHERAPY GROUPS*

	Single fraction (8 Gy x 1; n=80)		Multiple fractions (4 Gy x 6; n=86)		*P-value*
	Utilization†	Costs (95% CI)‡	Utilization§	Costs (95% CI)‡	
Costs of radiotherapy		2438 (2211 to 2665)		3311 (2950 to 3672)	<0.001
Initial treatment		1838 (1838 to 1838)		2448 (2448 to 2448)	0.000
Retreatments £12 weeks	18%	466 (266 to 666)	5%	159 (43 to 275)	0.01
Time, travel, out-of-pocket	10 h	134 (87 to 181)	25 h	704 (396 to 1012)	<0.001
Other medical costs		2072 (1231 to 2913)		3114 (1819 to 4409)	0.18
Hospitalization	28%	914 (226 to 1602)	41%	2160 (912 to 3408)	0.08
Systemic therapy	61%	373 (213 to 533)	59%	247 (145 to 349)	0.19
Consultations	6.3	302 (179 to 425)	6.4	248 (198 to 298)	0.42
Pain medication		79 (54 to 104)		56 (32 to 80)	0.19
Other medication		322 (131 to 513)		247 (133 to 361)	0.51
Home nursing care	5 h	81 (25 to 137)	9 h	156 (49 to 263)	0.22
Other non-medical costs		190 (-84 to 464)		28 (-289 to 345)	0.44
Time, travel	8 h	94 (41 to 147)		130 (74 to 186)	0.35
Out-of pocket		127 (42 to 212)		64 (22 to 106)	0.19
Domestic help	42 h	438 (302 to 574)	43 h	482 (339 to 625)	0.65
(Un)paid labor	56 h	-468 (-656 to -280)	77 h	-647 (-903 to -391)	0.26
Medical costs		4376 (3523 to 5229)		5720 (4403 to 7037)	0.09
Societal costs		4700 (3721 to 5679)		6453 (4869 to 8037)	0.06

* *Gy= gray; CI= confi dence interval= average ± x ($t_{n,0.05}$ $^{1/2}$) x standard deviation; P values derived from standard two-sided unequal-variance t tests*

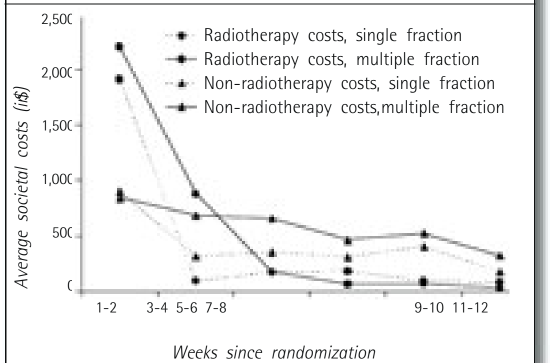
† *Percentage of patients receiving particular care, total number of consultations, or hours of care*

‡ *Average costs in $. Costs were derived from Dutch standard prices[17,18]*

§ *Negative costs represent profi ts*

FIGURE 3

Average societal costs for the single and multiple fraction radiotherapy groups. Radiotherapy costs refer to the medical and nonmedical costs of radiotherapy. Nonradiotherapy costs refer to all other societal costs (medical and nonmedical nonradiotherapy costs). Single fraction therapy refers to a single fraction of 8 Gy. Multiple fraction therapy refers to six fractions of 4 Gy. Weeks since randomization refers to the time the patients were enrolled in the Dutch Bone Metastasis Study.



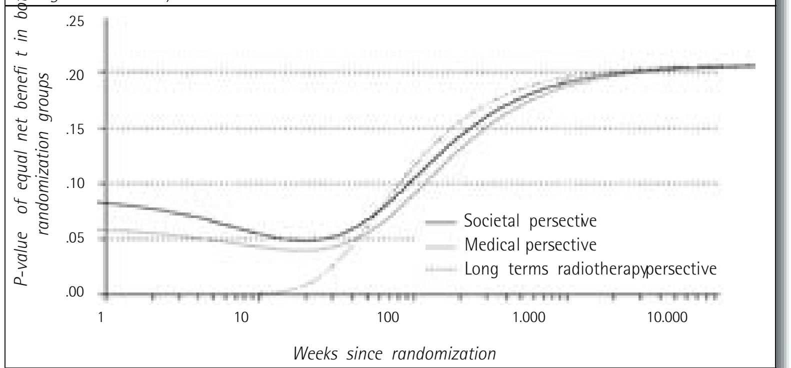
Because the differences in initial pain score and sex *(Table 1)* could have infl uenced the comparison, we performed a multivariate regression analysis of the estimated radiotherapy costs, the medical costs, and the societal costs. After adjusting for the randomization schedule, costs were not statistically signifi cantly predicted by the initial pain score (P = 0.37, P = 0.95, and P = 0.60, respectively) or by sex (P = 0.66, P = 0.52, and P = 0.38, respectively). Also, the estima ted QALYs of the patients who fi lled out the cost questionnaires did not differ from the estimated QALYs in the entire sample (P = 0.25 for the single fraction group and P = 0.95 for the multiple fraction group).

Cost-utility analysis

The estimated QALYs and societal costs both favored the single fraction treatment schedule, providing an additional 1.7 quality-adjusted weeks and saving $1753 relative to the multiple fraction schedule, although in neither case was

FIGURE 4

P values derived from testing the hypothesis of equal net benefi t (willingness-to-pay x quality-adjusted life years [QALYs] – costs) in both randomization groups, plotted in acceptability curves using standard two-sided unequal-variance t tests. Statistically signifi cantly better cost-effectiveness of the single fraction treatment schedule is demonstrated if the curve is below .05. The societal perspective includes all costs incurred during the fi rst 12 weeks after randomization. The medical perspective includes all medical costs of radiotherapy and of other health care during the fi rst 12 weeks after randomization. The long-term radiotherapy perspective includes all medical and nonmedical costs of radiotherapy during the fi rst 2 years after randomization.



the difference statistically signifi cant. Consequently, the single fraction schedule is likely to be more cost-effective than the multiple fraction schedule. The statistical certainty of this statement depends, however, on the relative value of QALYs compared with the relative value of money; that is, on how much one is willing to pay per QALY. If, on the one hand, QALYs are infi nitely more valuable than money, then comparing cost–utility reduces to comparing QALYs (*Table 2*, P = 0.21). If, on the other hand, money is infi nitely more valuable than QALYs, then comparing cost–utility reduces to comparing societal costs (*Table 4*, P = 0.06).

It is diffi cult to say how much society is willing to pay for a QALY. A rule of thumb that is often quoted in the international literature is that $ 50 000 per QALY is acceptable, whereas $ 100 000 per QALY might not be acceptable.[22] We tested cost-effectiveness by comparing the net benefi t in both randomization groups: the better cost-effectiveness of the single fraction treatment schedule is demonstrated if the net benefi t in the single fraction group is statistically signifi cantly better than that in the multiple fraction group. The derived P values for different levels of the willingness-to-pay were then plotted in acceptability curves (*Fig. 4*). From a societal perspective, the better cost-effectiveness of the single fraction radiotherapy was statistically signifi cant if one values a QALY between $ 5000 and $ 40000. When a QALY is valued at less than $ 5000 or more than $ 40000, then better cost-effectiveness of the single fraction schedule was still likely but no longer statistically signifi cant. For example, at $ 50000 and $ 100000 per QALY, the statistical signifi cance was P = 0.06 and P = 0.09, respectively.

We also performed a sensitivity analysis, considering different cost perspectives. From a medical cost perspective, the P values were somewhat less favorable than from the societal cost perspective and remained above the 5% statistical signifi cance level (*Fig. 4*). Restricting costs to the short- and long-term costs of radiotherapy, the better cost-effectiveness of the single fraction schedule was statistically signifi cant for all willingness-to-pay values less than $ 40000. This range was comparable to that obtained from the societal perspective.

Discussion

The Dutch Bone Metastasis Study showed that single fraction radiotherapy, even though it had a higher retreatment rate, was in many respects comparable to multiple fraction radiotherapy, with no statistically signifi cant differences identifi ed in pain response, analgesic consumption, treatment side effects, or quality of life.[9] These results have good external validity resulting from the large number of participating institutions and the diverse patient population.

In the cost–utility analysis presented here, effectiveness was measured by quality-adjusted life expectancy; that is, the overall valuation of health. Again, we found no statistically signifi cant difference between single and multiple fraction radiotherapy. The average nonadjusted life expectancies were 43.0 weeks for the single fraction schedule and 40.4 weeks for the multiple fraction schedule, which was not a statistically signifi cant difference. The societal value of these life expectancies was assessed using the EQ-5D questionnaire, taking into account mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Besides these general attributes, there are other issues that are also specifi cally relevant in the valuation of end-of-life care.[23] For example, psychosocial outcomes such as relieving the burden of care and strengthening relationships with loved ones are not included in the EQ-5D. Unfortunately, however, no valuation instrument exists that incorporates these specifi c end-of-life issues. Moreover, we noted a distinct decrease of the EQ-5D utility over time, especially toward the end of life, suggesting that the instrument is responsive to the changing health status of these patients. On the basis of the EQ-5D measurements, the average quality-adjusted life expectancies were 17.7 weeks in the single fraction group and 16.0 weeks in the multiple fraction group, which was not a statistically signifi cant difference.

From the patient perspective, it is obvious that a single fraction schedule is less burdensome than a multiple fraction schedule. The one outcome measure in our study that could make patients favor the multiple fraction over a single fraction treatment schedule is the probability of retreatment: 7% for the multiple fraction group versus 25% for the single fraction group. Although this is a considerable difference, an extra single fraction may still be experienced as less burdensome by most patients than a multiple fraction schedule. Furthermore, we believe that the difference in retreatment is not so much caused by inadequacy of the single fraction schedule, but more by the doctors' opinions on expected effectiveness and tolerance after the single dose. During the study, radiation oncologists seemed reluctant to accept the single fraction schedule as a reliable treatment. Compared with the multiple fraction group, patients in the single fraction group were retreated at a lower pain score (6.8 versus 7.5 in the single- and multiple fraction groups, respectively).[9]

The costs of radiotherapy for the single and the multiple fraction radiotherapy schedules, including retreatments and nonmedical costs of radiotherapy, were estimated at $ 2438 and $ 3311, respectively. Including other societal costs increased the estimated costs to $ 4700 for single fraction radiotherapy and $ 6453 for multiple fraction radiotherapy, a difference of $ 1753. Because the estimated societal costs and the quality-adjusted life expectancy were both favorable for single fraction radiotherapy, the combined cost-effectiveness clearly favors this treatment schedule. For willingness-to-pay between $ 5000 and $ 40000 per QALY, the better cost-effectiveness of the single fraction schedule was statistically significant relative to the multiple fraction schedule. The reliability of these estimates may be less for radiotherapy institutions outside The Netherlands because costs can vary substantially by country or even by radiotherapy institution.

Efficient use of the available treatment capacity is an important issue because new types of radiotherapy techniques, such as conformal radiotherapy and intensity-modulated radiotherapy,[24,25] require skilled personnel and more treatment time per patient. Moreover, as the population ages, the number of patients increases. As a result of the trial and facilitated by the fact that in The Netherlands the financial reimbursement is not directly proportional to the number of fractions prescribed,[26] all 21 Dutch radiotherapy institutions have adopted single fraction radiotherapy as their standard treatment.[27] The reduction of the waiting time resulting from insufficient treatment capacity, rather than lower costs, is considered the major economic advantage to single fraction radiotherapy.[9,28] In The Netherlands, the annual number of radiotherapy treatments is approximately 40000,[28] with a total of approximately 640000 fractions. Because 10% of the treatments are palliative radiotherapy for patients with painful bone metastases and because before the Dutch Bone Metastasis Study such patients, on average, received six fractions per treatment, using only single fraction schedules saves approximately 3% of the national linear accelerator capacity and departmental workload.

Controversial medical decisions are often those that are made in a field of conflicting interests. We believe this is not the case here. Compared with multiple fraction therapy, single fraction therapy provides equal palliation to patients and reduces the number of journeys to the hospital. Single fraction therapy is more easily included into departmental schedules, reducing both medical and societal costs and saving treatment capacity for other patients. Therefore, single fraction radiotherapy should be considered as standard palliative treatment for patients with painful bone metastases.

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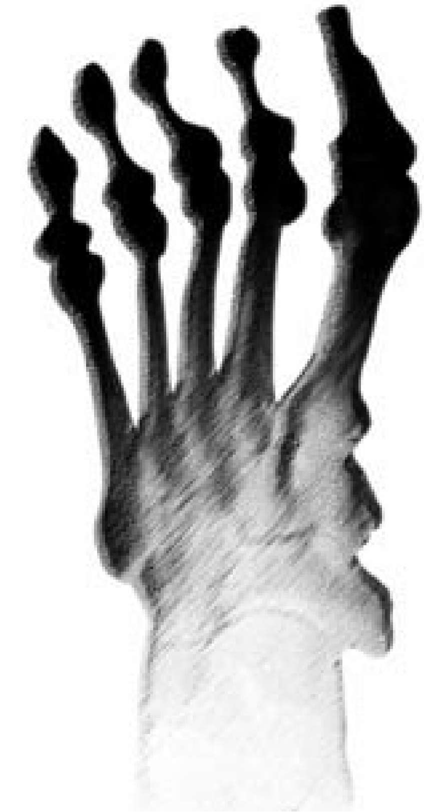

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Discussion and future perspectives