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Enayatollah Homaie Rad

Guilan University of Medical Sciences

Mehdi Javanbakht

Newcastle University

Amir Hashemi Meshkini

Tehran University of Medical Sciences

Pardis Zaboli

Tehran University of Medical Sciences

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Cost-Utility Analysis of Single-Fraction Versus Multiple-Fraction Radiotherapy in Patients with Painful Bone Metastases: An Iranian Patient's Perspective Study

Yahya Bayazidi[1], *Ali Keshtkaran*[2,*], *Enayatollah Homaie Rad*[3], *Mansour Ansari*[4], *Mehdi Javanbakht*[5], *Amir Hashemi Meshkini*[6], *Shokoufeh Nikfar*[6], *Pardis Zaboli*[6]

[1]Student Research Committee, School of Health Management and Informatics, Shiraz University of Medical Sciences, Shiraz, Iran; [2]School of Health Management and Informatics, Shiraz University of Medical Sciences, Shiraz, Iran; [3]Social Determinants of Health Research Center, Guilan University of Medical Sciences, Rasht, Iran; [4]Shiraz University of Medical Sciences, Shiraz, Iran; [5]Health Economics Unit, School of Health Management and Informatics, Shiraz University of Medical Sciences, Shiraz, Iran; [6]School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

A B S T R A C T

Objectives: To evaluate two of the various treatment strategies of bone metastasis— single-fraction radiotherapy and multiple-fraction radiotherapy. **Methods:** A multistage Markov decision model was applied to assess the incremental costs per quality-adjusted life-year (QALY) gained of single fraction against multiple fractions. The model had a monthly cycle length over a lifetime horizon with 1000 hypothetical cohort samples. The EuroQol five-dimensional questionnaire was used to estimate the health-related quality of life in patients. To cope with parameters of uncertainty, we conducted a probabilistic sensitivity analysis using a Monte-Carlo simulation technique. Both cost and utility variables were discounted by 3% in the base model. Strategies were assessed considering a willingness-to-pay threshold of US $6578 per QALY gained. **Results:** The expected mean cost and quality-adjusted life-years were, respectively, US $447.28 and 5.95 months for patients receiving single-fraction radiotherapy and US $1269.66 and 7.87 months for those receiving multiple-fraction radiotherapy. The incremental cost-utility ratio was US $428.38 per QALY. Considering the Iranian gross domestic product per capita (US $6578) as the recommended willingness to pay for 1 QALY gained, the multiple-fraction method was found to be a cost-effective strategy. **Conclusions:** Policymakers should advocate the multiple-fraction method instead of the single-fraction method in the treatment of patients with painful bone metastases.

Keywords: bone metastasis, cost-utility analysis, Markov modeling, Monte-Carlo simulation, radiotherapy.

Introduction

Cancer is one of the leading causes of mortality in the world with an increasing trend of prevalence. So it is important to increase the financial resources of the health system for cancer care [1].

Cancers are the third leading cause of death in Iran after cardiovascular diseases and accidents. Because of the growing number of patients with cancer across the world, and even in Iran, today, cancer is a major problem for health systems. Furthermore, the growing death rate is the reason for more than 12% of deaths. Statistics show that the annual incidence of cancer in Iran is more than 70,000 [2], and more than 35,242 people die from cancers yearly [3]. With an increase in life expectancy and in the proportion of the aging population in Iran, it is expected that the prevalence of cancer will be doubled in the next two decades [4].

Approximately 60% of patients with cancer will experience metastasis during their illness [5]. Bone metastasis occurs in 70% of patients with prostate cancer and 30% of patients with lung, bladder, and thyroid cancers. This complication involves severe pain, metastatic spinal cord compression, pathological fractures, limitation in walking, drowsiness, and a significant decrease in quality of life [6]. A number of palliative treatments are available for treating bone metastatic cancer, including local therapy (external beam radiotherapy), systemic therapy (chemotherapy, systemic radionuclides, or bisphosphonates), and conservative treatment with pain medication. Palliative treatment choices depend on the cancer type and stage, the patient's age and health status, and the physician's discretion [7–9].

Patients with metastatic cancer need to be evaluated immediately for radiotherapy treatment because of the following reasons:

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* *Address correspondence to*: Ali Keshtkaran, Faculty of Management and Medical Information, Shiraz University of Medical Sciences, Shiraz, Iran.

E-mail: keshtkaa@sums.ac.ir

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1. The bone pain caused by metastatic cancer is one of the most common syndromes that require treatment.
2. Patients with bone metastasis have more survival time than do those with visceral metastasis and so they experience disease complications for a longer time.
3. These patients have longer trouble and discomfort time than do patients with liver or lung metastasis and the disease develops earlier.
4. Bone metastasis complications are common (in one-third of patients) and will lead to severe disabilities.
5. Many problems are associated with the care of these patients [10–12].

In the past two decades, clinical evidence suggested that short-term treatment strategy or single radiation therapy (SRT) and long-term treatment strategy or multiple radiation therapy (MRT) have similar efficacy on controlling symptoms in patients with incurable cancer, especially in those with painful bone metastases [8,13,14].

In the single-fraction method, the total amount of radiation received by the patient is less and is given a limited number of times, but in the multiple-fraction method, the total amount of radiation received by the patient is high on a low dose in any fraction schedule used to achieve high local control of symptoms [15–17].

In the short-term treatment strategy, the number of visits is increased and the waiting time for radiotherapy is decreased. Evidence showed that in some clinical status, the long-term treatment (MRT) can be more effective than the short-term treatment (SRT) [18]. Patients with advanced cancer under a good treatment condition have higher life expectancy and these often occur in long-term palliation treatment (MRT) with a much higher amount of total dose irradiation [11,19,20].

Without palliative therapy, about 79% of patients will experience severe pain [7]. In some studies in Iran, the benefits of the two methods have been measured and evaluated [18]. According to the health policy perspective, the budget constraint of these treatments must be noticed and made more effective, and the lowest cost must be defined. For this purpose, one of the best methods is to conduct a cost-effectiveness analysis, which measures the benefits as well as costs [21].

The aim of this study was to perform an economic analysis comparing the single-fraction method with the multiple-fraction method for the first time in an Iranian setting.

Methods

We used a previously published Markov model [22] for evaluating the cost-utility analysis of multiple fractions compared with that of a single fraction in the treatment of patients with painful bone metastases. The model used a monthly cycle length for a 5-year time horizon with 1000 hypothetical cohort samples. The EuroQol five-dimensional questionnaire (EQ-5D) was used to measure the quality of life of the patient and a Markov Monte-Carlo simulation method was used to compare the two methods.

The monthly transition probability assuming constant rates was calculated by using the following equation:

Monthly rate=[- ln(1 - Probe)/Time].

And the monthly probability of occurrence was calculated by using the following formula:

Monthly probability = 1−*exp*(−Monthly rate).

Study Population

Through a pilot study the sample size for our study was estimated to be 100 patients. All the patients were referred to the Oncology and Radiotherapy Department of the Namazi Hospital in Shiraz between 2012 and 2013. Our inclusion criteria were as follows: 1) the patient had bone metastasis pain; 2) the patient was undergoing radiotherapy and oncology treatment continuously; 3) the patient was registered in the data register; 4) the patient had not undergone radiotherapy before; and 5) the patient's pain score was between 7 and 10, which represented severe pain on the Brief Pain Inventory. All the patients had signed the informed consent form and none of them was excluded during the study. The patients were divided into two groups on the basis of the type of therapy, and then within each group they were further categorized on the basis of the registry number. The samples were selected randomly among 247 patients.

Single- and Multiple-Fraction Radiation Therapy Models

The models for both single fraction and multiple fractions were the same, as shown in Figure 1. The models were designed on the basis of the diagnostic stages of the disease and potentially had six states: No pain state 1 (after initial treatment), Pain medication (using MRT, SRT, or re-treatment), No pain state 2 (after re-treatment), and Death.

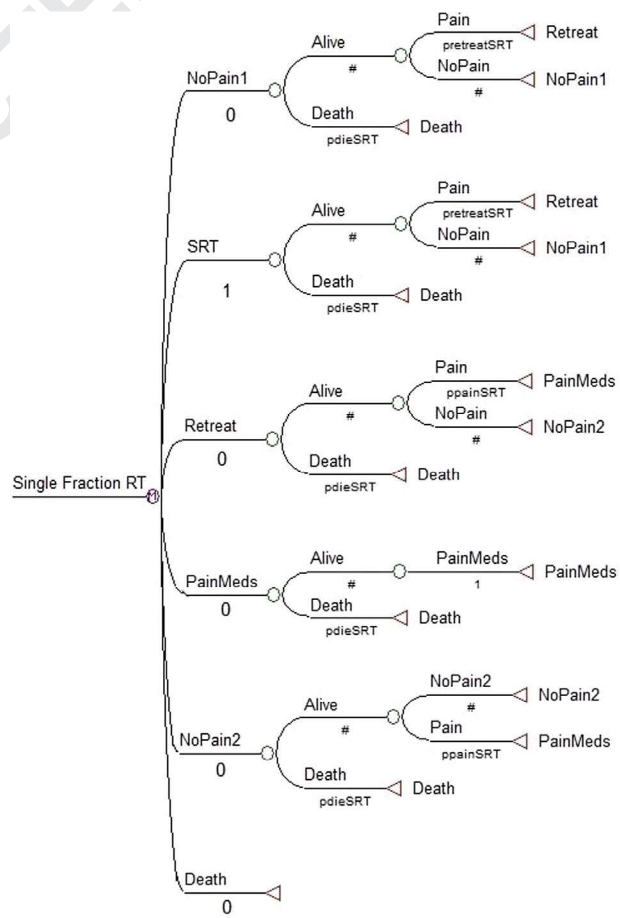

Fig. 1 – The model for both SRT and MRT. MRT, multiple radiation therapy; RT, radiotherapy; SRT, single radiation therapy.

Death was the absorbing state in both models. If the patients were alive and experiencing pain, they were re-treated using the same fractionation method [23]. If there was pain relief, the patients entered into the No pain state 1. These patients could either remain without pain or have pain and be re-treated. Patients undergoing re-treatment could remain without pain and enter into the No pain state 2, or if they had pain, they entered into the Pain medication state and stayed there until death. Patients in the No pain state 2 could remain without pain or if pain returned, they entered into the Pain medication state. In the Pain medication state, patients used medications to relieve pain. Medications included aspirin, acetaminophen or a non-steroidal anti-inflammatory drug, and opioids (morphine, methadone, hydromorphone, oxycodone, fentanyl, and tramadol). Other medications may be used at the same time the patient takes pain medication.

This is to intensify the effectiveness of pain medications, reduce symptoms, and relieve specific types of pain. These drugs include antidepressants, corticosteroids, local anesthetics, anticonvulsants, bisphosphonates, and stimulants. Both cost and utility parameters were discounted by 3% in the base model.

Transition Probabilities

The overall survival rate obtained from the literature at 3 years was 5% and 17%, respectively, for male and female patients receiving single fraction, and 10% and 23%, respectively, for male and female patients receiving multiple fractions [6–12]. The probability of pain at 1 year ranged from 47% to 50% for the SRT group and from 40% to 50% for the MRT group. The re-treatment rate was 10% to –11% for the MRT group and 22% to –23% for the SRT group [22,24]. Distributions were sampled for each state transition probability using a second-order Monte-Carlo simulation technique for survival, re-treatment rates, and pain relief from the literature. State transition probabilities were modeled using a beta distribution. Beta distributions are frequently used to represent distributions for transition probabilities and utilities. Beta distributions are bounded by 0 and 1. Sensitivity analyses were performed on the cost, transition probabilities, and utility values. At the end of the study, to have an obvious result a cost-effectiveness probability curve based on willingness to pay (WTP) was also plotted.

Calculating Utility

We used the EQ-5D for measuring the quality of life of the patients and the Brief Pain Inventory (BPI) form for estimating patients' pain. We also designed a checklist to collect the socio-economic and other characteristics of the patients.

The utility values for our study were extracted from the EQ-5D. The EQ-5D is a generic, standard, and preference-based questionnaire that is used to indirectly extract utility values. This questionnaire consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which has three levels of response (no problems, some problems, and extreme problems). It covers a total of 243 health states. Scoring is based on a range from –0.59 to 1.00, with 0 representing dead, 1 indicating a state of full health, and negative scores representing health states that are perceived to be worse than death. The reliability of the EQ-5D was calculated and confirmed in Iran [25].

The BPI questionnaire was developed for cancer-related pain and its validity and reliability have been confirmed in Iran [26]. It measures the characteristics of pain: first, the intensity of pain, which is called the sensory dimension, and second, the interference of pain in the patient's life, which is called the reactive dimension. In the BPI, the patient is questioned about the severity of the pain in the last 24 hours. Its scores are between 0 and 10, with 0 indicating no pain and 10 the most imaginable pain. A score between 7 and 10 represents severe pain on the BPI. The reason of using this questionnaire is to exclude patients with low pain from the study.

For each patient, the utility was calculated using the EQ-5D. Two facilitators were trained to implement the two questionnaires. An annual discount rate of 3% was considered for this study.

Calculating Costs

In the health care system of Iran, the cost of cancer treatment for patients is very high, but because most patients are covered by different types of health insurances, and usually the entire cost of radiotherapy is paid out by insurance, the perspective was formed on the basis of the costs imposed on health systems because of radiotherapy services. Therefore, we took a health care system perspective and thus considered only the intervention costs and the direct medical costs associated with the disease. We designed a checklist for calculating the costs for patients.

For all patients the usage of services was calculated by using the microcosting method and this required a review of the patients' hospital records to determine what type of services were used and the allocation of costs for each service.

The modeled costs were sampled using a range of costs listed in Table 1. The costs were then converted from Iranian rial to US dollar using the exchange rate of 24730 rials.

After calculating the costs and utilities, we calculated the incremental cost-utility ratio. Because of the uncertainty in economic evaluation, we tested the reliability and validity of our results. To do so, we conducted sensitivity analyses along with deterministic and probabilistic sensitivity analyses using the TreeAge pro-2011 software (TreeAge Software, Inc., Williamstown, MA).

Results

Of the 100 patients, 41 patients underwent single-fraction palliative radiotherapy and 59 patients underwent multiple-fraction palliative radiotherapy.

Of these patients, 46% were women, their age ranging between 20 and 83 years: 24% were younger than 35 years, 31% were between 35 and 50 years, and the remaining (45%) were older than 50 years. Thirteen patients (13%) were illiterate, 34 patients (34%) were in high school, 30 patients (30%) had a diploma, and 23 patients (23%) were graduates. The sites of treatment included bone marrow (28 patients), extremities (19 patients), humerus (9 patients), sacrum (14 patients), ribs (5 patients), and spine (25 patients). No significant differences were found between the two groups in terms of sex, age, and degree of pain before and after treatment ($P > 0.1$), but differences were significant for income and education.

Table 1 presents the mean cost of each Markov state in radiotherapy. We calculated the direct costs of the treatment for each patient. For evaluating costs, we followed up each patient during the treatment and checked the services they used. We then totaled the cost allocated to each service to determine the total cost.

We calculated the mean costs for a lifetime horizon using the Markov model as well as life expectancy and life tables. The mean costs were US $447.28 and US $1269.66 for patients receiving single fraction and multiple fractions, respectively. The mean quality-adjusted life-year for patients undergoing single-fraction treatment was 5.95 months, and for patients undergoing

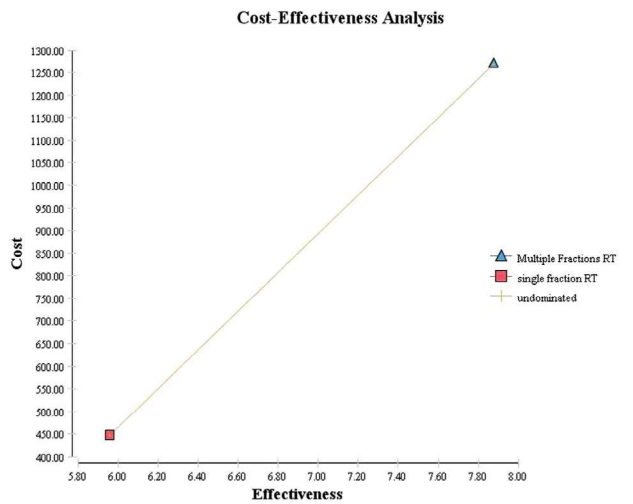

Fig. 2 – The cost-effectiveness of MRT in comparison with SRT. MRT, multiple radiation therapy; RT, radiotherapy; SRT, single radiation therapy.

multiple-fraction treatment it was 7.87 months. Therefore, the incremental cost-effectiveness ratio (ICER) was US $428.38 per 1 quality-adjusted life-year. Figure 2 shows the cost-effectiveness (F2) of multiple fractions in comparison with single fraction. The results showed that the patients receiving multiple fractions had more utility and costs.

Sensitivity Analysis

The parameters and the range of values used in the sensitivity analysis are presented in Table 1. The distribution type is also presented. (QF3 Q8) Figure 3 shows the results of the one-way sensitivity analysis. The sensitivity analysis variables were as follows: quality of life with pain medication for SRT, quality of life with no pain in SRT, quality of life with pain medication for MRT, quality of life with no pain in MRT, cost of treatment for MRT, cost of treatment for SRT, quality of life for SRT, and quality of life for MRT. The effects of changes in the ICER are shown as a sensitivity analysis. As shown in the figure, the marginal

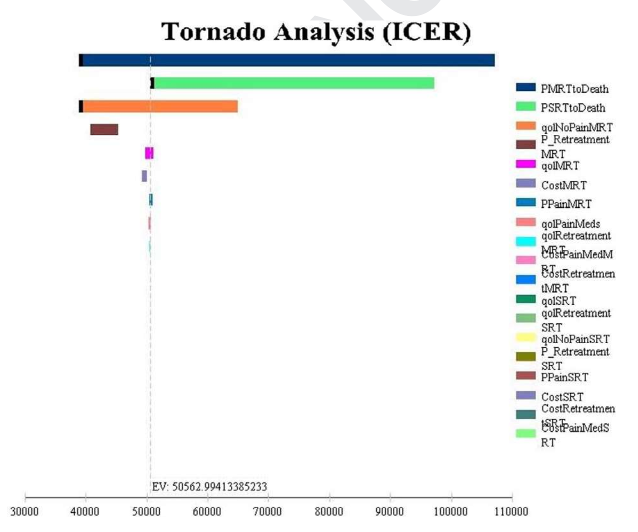

Fig. 3 – The results of one-way sensitivity analysis. ICER, incremental cost-effectiveness ratio; MRT, multiple radiation therapy; RT, radiation therapy; SRT, single radiation therapy.

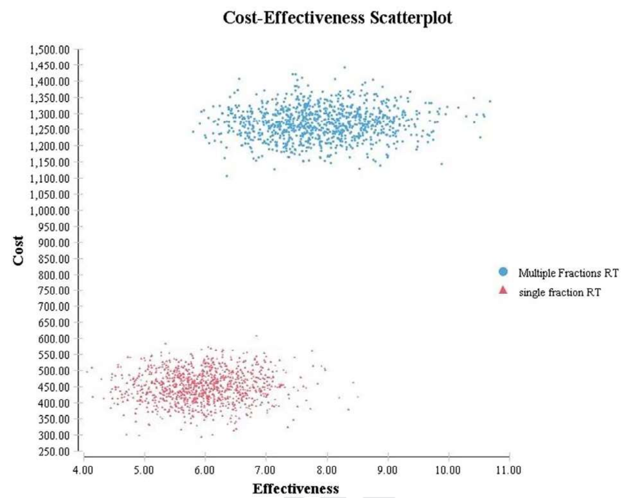

Fig. 4 – The results of Monte-Carlo simulations. RT, radiotherapy.

outcome is sensitive to the probability of MRT to death, the probability of SRT to death, the quality of life with no pain for MRT, the probability of re-treatment, quality of life for MRT, and cost of MRT. Other variables do not have significant effects on the ICER. At the end, we performed a probabilistic sensitivity analysis. This analysis is for model-based economic evaluations and is conducted with distributed parameters. Figure 4 shows the (F4) results of this analysis. Several ICERs were calculated using Monte-Carlo simulation. A total of 1000 points were calculated and marked in the figure and the distribution curve was plotted.

Figure 5 shows the results of the ICERs calculated using (F5) Monte-Carlo simulation. It also shows the number of points marked in each quadrant. We used US $6578 as a threshold (gross domestic product per capita in 2011 for Iran). With these assumptions, 94.7% of the points were placed in quadrant I (with positive cost and positive utility) and 5.3% of the points were placed in quadrant II (with positive cost and negative utility). This means that multiple-fraction method is better than the single-fraction method from the point of view of cost-utility analysis. The cost-effectiveness acceptability curve in Figure 6 reflects the (F6) better method to use. As shown in the figure, at lower WTP, the SRT method was better than the MRT method, but at higher WTP,

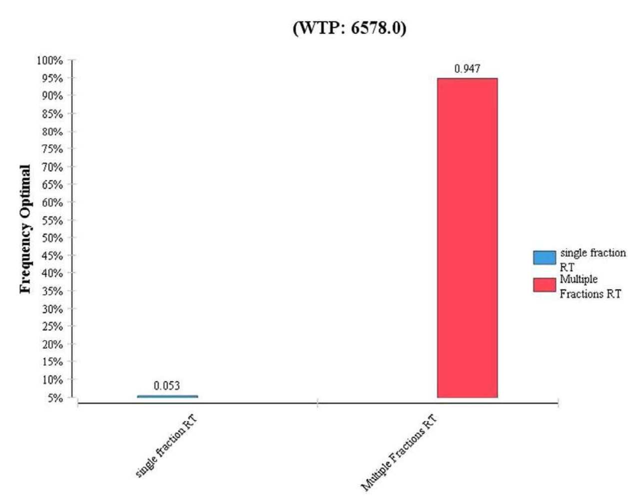

Fig. 5 – Monte-Carlo strategy selection. RT, radiotherapy; WTP, willingness to pay.

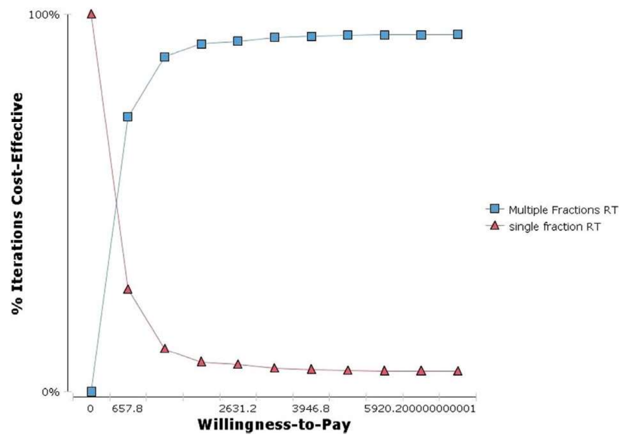

Fig. 6 – The cost-effectiveness acceptability curve. RT, radiotherapy.

the MRT was a better method. The probability of MRT being a better method at higher WTP was 94.7%.

Discussion

This study showed that MRT was cost-effective compared with SRT because of less re-treatment in MRT. Similar to this study, Konski et al. [22] found that at lower WTP, SRT was a cost-effective method, but at higher WTP, MRT was better.

We found that the multiple-fraction method is better than the single-fraction method. The single-fraction method is cheaper but its utility is lower too. In 2003, van den Hout et al. [27] compared these two radiotherapy methods by performing a cost-utility analysis. Their study included 1157 patients and the quality of life was calculated by using the EQ-5D. The results of this study showed that no significant differences existed between the two treatment methods in terms of quality of life and life expectancy, but the costs of the single-fraction method were lower than those of the multiple-fraction method. In a systematic review and meta-analysis, Wu et al. [28] in 2004 compared the effects of the single-fraction method with those of the multiple-fraction method. They did not find any differences in these two methods in terms of decrease in pain. Barton et al. [29] calculated the actual costs and quality of life in patients with bone metastasis in Australia. Hospital records between 1991 and 1996 were reviewed in this study. The total costs per total number of response months were calculated to find the cost-utility ratio. The per month utility of bone metastasis was found to be A$100 or A$1200 per utility-adjusted life-year. In a study done by Sze et al. [30], the researchers used a meta-analysis to compare the single-fraction method with the multiple-fraction method. The results showed that the single-fraction method was as effective as the multiple-fraction method in decreasing metastatic bone pain, but the re-treatment rate was higher for the single-fraction method.

Considering the perspective of Iranian patients with bone metastasis and a WTP threshold of US $6578, both studied methods were found to be cost-effective, but we recommend using the multiple-fraction method. The incremental cost-utility ratio for the chosen method was US $428.38, indicating that this treatment method has high priority in our health system and thus policymakers should consider and recommend it instead of the single-fraction method. This policy can contain the waste of resources and lead to the use of resources in other needed health fields.

Study Limitations

This study had some limitations. Because the target population consisted of patients with cancer, these patients were physically and psychologically not in a good condition to answer questionnaires. The samples had been collected from a public hospital and hence generalizability of study findings to other areas and centers should be performed with caution. Considering the fact that only direct medical costs were considered, our findings may not be directly comparable with other studies.

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REFERENCES

[1] Micheli A, Coebergh JW, Mugno E, et al. European health systems and cancer care. Ann Oncol 2003;14(Suppl. 5):v41–60.

[2] Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Poor glycemic control predicts coronary heart disease events in patients with type 1 diabetes without nephropathy. Arterioscler Thromb Vasc Biol 1999;19:1014–9.

[3] Mousavi SM, Gouya MM, Ramazani R, et al. Cancer incidence and mortality in Iran. Ann Oncol 2009;20:556–63.

[4] Hatam N, Ahmadloo N, Daliri AAK, et al. Quality of life and toxicity in breast cancer patients using adjuvant TAC (docetaxel, doxorubicin, cyclophosphamide), in comparison with FAC (doxorubicin, cyclophosphamide, 5-fluorouracil). Arch Gynecol Obstet 2011;284:215–20.

[5] Anderson PR, Coia LR. Fractionation and outcomes with palliative radiation therapy. Semin Radiat Oncol 2000;10:191–9.

[6] International Atomic Energy Agency. Criteria for Palliation of Bone Metastases—Clinical Applications. Vienna, Austria: International Atomic Energy Agency, 2007.

[7] Janjan NA, Payne R, Gillis T, et al. Presenting symptoms in patients referred to a multidisciplinary clinic for bone metastases. J Pain Symptom Manage 1998;16:171–8.

[8] Steenland E, Leer J, van Houwelingen H, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. Radiother Oncol 1999;52:101–9.

[9] Hartsell WF, Santosh Y. Palliation of bone metastases. In: Halperin EC, Perez CA, Brady LW, eds., Principles and Practice of Radiation Oncology (5th ed.). 2008; 1986–99.

[10] Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short-versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst 2005;97:798–804.

[11] Powers W, Ratanatharathorn V. Palliation of bone metastases. In: Perez CA, Brady LW, eds., Principles and Practice of Radiation Oncology. Philadelphia, PA: Lippincott-Raven Publishers, 1997; 2199–218.

[12] Price P, Hoskin P, Easton D, et al. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. Radiother Oncol 1986;6:247–55.

[13] Yarnold J. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. Radiother Oncol 1999;52:111–21.

[14] Kanjeekal S, Chambers A, Kee Fung M, Verma S. Systemic therapy for advanced uterine sarcoma: a systematic review of the literature. Gynecol Oncol 2005;97:624–37.

[15] Ratanatharathorn V, Powers W, Temple H. Palliation of bone metastases. In: Perez CA, Brady LW, Halperin EC, Schmidt-Ulrich RK, eds., Principles and Practice of Radiation Oncology. (4th ed.). Philadelphia, PA: Lippincott Williams & Wilkins, 2004; 2385–404.

[16] Lawrence TS, Ten Haken RK, Giaccia A. Principles of radiation oncology. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, eds., Cancer: Principles and Practice of Oncology. (8th ed.). Philadelphia, PA: Lippincott Williams and Wilkins, 2008.

[17] Patel RR, Arthur DW. The emergence of advanced brachytherapy techniques for common malignancies. Hematol Oncol Clin North Am 2006;20:97–118.

[18] Amouzegar-Hashemi F, Behrouzi H, Kazemian A, et al. Single versus multiple fractions of palliative radiotherapy for bone metastases: a randomized clinical trial in Iranian patients. Curr Oncol 2008;15:151.

[19] Gaze MN, Kelly CG, Kerr GR, et al. Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. Radiother Oncol 1997;45:109–16.

[20] Niewald M, Tkocz H-J, Abel U, et al. Rapid course radiation therapy vs. more standard treatment: a randomized trial for bone metastases. Int J Radiat Oncol Biol Phys 1996;36:1085–9.

[21] Folland S, Goodman A, Stano M. Economics of Health and Health Care. Upper Saddle River, NJ: Pearson, 2006.

[22] Konski A, James J, Hartsell W, et al. Economic analysis of Radiation Therapy Oncology Group (RTOG) 97-14: multiple versus single fraction radiation treatment of patients with bone metastases. Am J Clin Oncol 2009;32:423.

[23] Chow E, Hoskin P, Wu J, et al. A phase III international randomised trial comparing single with multiple fractions for re-irradiation of painful bone metastases: National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) SC 20. Clin Oncol 2006;18:125–8.

[24] Konski A, DeSilvio M, Hartsell W, et al. Continuing evidence for poorer treatment outcomes for single male patients: retreatment data from RTOG 97-14. Int J Radiat Oncol Biol Phys 2006;66:229–33.

[25] Adib HM, Abbasinia M. Assessing quality of life of elders with femoral neck fractures, using SF36 and EQ5D. Iran J Nurs Res 2010;4:71–9.

[26] Vakilzadeh P, Nakhaei N. The reliability and validity of the Persian version of the Brief Pain Inventory in cancer patients. J Rafsanjan Univ Med Sci Health Serv 2007;4:5.

[27] van den Hout WB, van der Linden YM, Steenland E, et al. Single-versus multiple-fraction radiotherapy in patients with painful bone metastases: cost–utility analysis based on a randomized trial. J Natl Cancer Inst 2003;95:222–9.

[28] JS-Y Wu, Wong R, Johnston M, et al. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. Int J Radiat Oncol Biol Phys 2003;55:594–605.

[29] Barton MB, Jacob SA, Gebsky V. Utility-adjusted analysis of the cost of palliative radiotherapy for bone metastases. Australas Radiol 2003;47:274–8.

[30] Sze W, Shelley M, Held I, et al. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy—a systematic review of randomised trials. Clin Oncol 2003;15:345–52.