Clinicopathologic Characteristics and Survival of Patients With Bone Metastasis in Yazd, Iran

A Cross-Sectional Retrospective Study

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Abstract: To evaluate the clinico-pathological and survival characteristics in patients with bone metastasis.

This cross-sectional study was conducted on patients with bone metastasis who referred to Shahid Ramezanzadeh radiation oncology center. For all of the patients studied, demographic and survival information was recorded. SPSS was used to analyze the data.

In this study, 89 men (53.3%) and 78 women (46.7%) with bone metastasis were examined. Most of the patients were in the 66 to 87 age range. Breast cancer was the most common type of cancer in women and prostate cancer was the commonest in men. In most patients, pain was the first manifestation of the disease, and the spine has been most frequently involved areas. The disease was diagnosed by isotope bone scan in the most cases. The mean survival was 31.1 months for patients with breast cancer, 12.9 months for patients with prostate cancer, 13.7 months for patients with lung cancer and the overall survival was 22.5. There was only a meaningful correlation between sex, type of cancer, radiation dose, and survival in patients. We found that age was more effective than the variable of cancer type in survival of patients with bone metastasis.

The prognosis of patients with bone metastasis in our center is fair. There was a significant correlation between sex, type of cancer, radiation dose, and survival. Cox proportional hazards model showed that age was a predictor of death.

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Abbreviations: MMPs = matrix metalloproteinase, Gy = Gray (unit).

INTRODUCTION

One of the most common sites of metastasis in patients with cancer is bone.[1] There are several steps to develop bone metastasis. These stages include angiogenesis, focal invasion through the basement membrane, connection with vascular endothelium and target organ, and tumor cells removal from the inner part of the tissue. Simultaneous with these proceedings, matrix metalloproteinase (MMPs) are secreted by tumor cells.[2,3] The incidence rate of bone metastasis is greatly different in various cancers. For example, bone metastasis occurs in 70% of patients with breast and prostate cancer and it is also found in 85% of patients who die of breast and prostate cancer, whilst the occurrence of bone metastasis in patients with gastrointestinal cancer is reported between 3% and 15%.[4] Life expectancy for patients with bone metastasis has improved greatly in recent years. For this reason, the patients are at the risk of developing skeletal symptoms and complications including pain, decrease in activities, high blood calcium level, high blood pressure, and damage to nervous system such as spinal cord compression and fracture. Therefore, early detection of patients who are at risk and appropriate treatment can lead to improvement in patients' quality of life, reduction in treatment costs, the prevention of patients' disability and the prevention of life threatening complications.[5] A large number of bone metastases have no symptoms and are often found accidentally during first examinations or during patients' follow up. In the symptomatic cases, bone pain is the most common symptom. Standard techniques for detection of bone metastases are using imaging modalities including radiography and (99m) Tc-MDP bone scintigraphy.[6,7] Current treatment for bone metastasis includes analgesics to control the pain, radiation therapy (local or systematic), bisphosphonates and surgery. Since these patients are finally referred to radiation oncology centers, examining patients who referred to the Shahid Ramezanzadeh Radiotherapy Center – as the only center of radiotherapy-oncology in Yazd and centers of excellence in treating patients with cancer in south of Iran – can give us an index of demographic and clinicopathological characteristics in patients with bone metastasis in above-mentioned region. Detection of these characteristics enables physicians to search for proper treatment protocols and to provide the appropriate facilities for improving diagnosis and treatment of complications promoted by them.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences. The current study was a cross-sectional study in which the target populations were the patients with bone metastasis who referred to Shahid Ramezanzadeh Radiation Oncology Center in Yazd in the years between 2007 and 2012. Sampling was done by taking a census. The study's inclusion criterion was the evidence of bone metastasis in radioisotope scan and/or cross sectional radiological studies. Data were collected using the questionnaire based on the intended goals and it was done by the

researcher using the information in patients' records. Every patient had a file containing demographic characteristics, imaging and pathological findings. Then, according to his/her requirement, the patient underwent radiotherapy and/or systemic therapy according to the oncologists' decision. Radiation therapy was performed by using Cobalt 60 machine or 9MV photon of Nepton linear accelerator. All of them were treated with a two-dimensional technique and most of them with two parallel apposed fields. For 93 patients the dose of 30 Gray (Gy) in 10 daily fractions was given. Thirty one patients received the dose of less than 30 Gy (25 patients received the dose 20 Gy in 5 daily fractions and 6 patients received the dose 8 Gy in one day). Forty three patients received doses above 30 Gy (3750 cGy in 15 daily fractions). Except in fewer than 5 percent of the patients, Bisphosphanat was applied for patients before, simultaneously or after radiotherapy. Most of them received Zoledronic acid or Pamidronate every 28 days. Reradiation was used for 23 patients in this study. This modality was used when more than 3 months had past from the previous course of radiation therapy and the disease was under control in other sites, however the patients complained of bone pain. If the patient had been given the dose of 8 Gy in one fraction this time he (she) received 30 Gy in 10 daily fractions. Otherwise they received 10 to 20 Gy in 4 to 8 daily fractions. Patients' follow-up was done on the phone. Overall survival was calculated from the day of diagnosis of bone metastasis (according to radioisotope scan and/or radiological studies) to death or last visit. Through coordination with The Health Center of the Province, data on mortality demographics of patients was obtained, however information regarding other provinces was gathered through telephone contacts. The software of SPSS (version 16) was used to analyze the data.

RESULTS

The mean age of examining patients was 57.91 ± 15.19 years and the age limit was 27 to 87, and most of the patients were in the 66 to 87 age range. Of 167 patients who were studied, 89 persons were men (53.3%) and 78 persons were women (46.7%). Of these 167 patients with bone metastasis, 39 patients suffered from breast cancer, 37 patients had prostate cancer, 24 patients suffered from lung cancer and 67 patients were with other cancers (Figure 1). Of these 89 men, 37 (41%) were determined to be prostate cancer patients, 17 (19%) were diagnosed to be lung cancer patients and 7 (7/8%) were found to be gastrointestinal cancer patients. And of 78 women, 37 (47%) were determined with breast cancer, 11 (14%) were diagnosed with gastrointestinal cancer and 7 (8%) suffered from lung cancer. Pain was the first manifestation in 145 of the whole 167 patients with bone metastasis; neurologic symptoms were the earliest in 14 patients; and in 8 patients, pathologic fracture happened first. Of 167 patients who referred to this radiation oncology center and who were studied, 51 were determined with lumbar vertebrae involvement, 24 patients with thoracic vertebral involvement, 25 patients with pelvic involvement, 28 patients with lumbar and thoracic vertebral involvement, 16 patients with upper extremity involvement, 8 patients with lower extremity involvement and 15 patients with other parts of the skeletal involvement. In most patients (136), the disease was diagnosed by isotope bone scan, it was diagnosed by MRI in 27 patients and just in 4 patients the disease was detected by CT scan. Of 161 patients with bone metastasis, 31 patients received less than 30 Gy radiation dose in their first admission, whereas 93 patients received 30 Gy, and 37 patients received more than 30 Gy radiation dose. (The number of samples was reduced from 167 to 161 because the patients with a different survival from others were considered as outliers and were excluded from the data set). According to the patients' declaration, pain was reduced by applied treatments. In the years between 2007 and 2012, of 167 patients with bone metastasis 102 persons (61.1%) died and 65 persons were part of censored data, i.e. the data which have not achieved the intended event (By ''event'' we mean ''the death''). The results of Log-rank test showed that there was no meaningful relationship between the age of patients and their survival (Figure 2), whereas there was a significant difference between the gender of patients and their survival rate. The results of Log-rank test also showed a significant difference between the type of cancer and the patients' survival (Figure 3). In this study, Cox Regression was used to examine the ratio of risk of death to types of cancer, taking account of age and in the absence of taking account of age. In the absence of taking account of age, prostate cancer and lung cancer increased the risk of death in patients compared with breast cancer. Since we added the *age* variable to this study, *type of cancer* lost its impact, and there was no significant difference between prostate cancer and lung cancer compared with breast cancer (Figure 4). The results of Log-rank test indicated that there was a significant difference between the dosage of radiation and patients' survival (Figure 5). The results of Log-rank test also showed that there was no significant difference between the first manifestation of the disease and patients' survival. The results of Log-rank test demonstrated that there was no significant difference between anatomical site involved and patients' survival. Our study was not designed to investigate the relationship between survival and applied systemic treatments. The mean survival in breast cancer patients was 31.1 months, it was 12.9 months in patients with prostate cancer and it was 13.7 months in lung cancer patients. It was found that the mean survival was 22.5 months in patients with bone metastasis in general.

DISCUSSION

At the present time, the incidence rate for all cancers is increasing in our society. Methods of diagnosis and treatment for cancers are changing and developing constantly in a way that some of these cancers are even able to be cured in early stages. The burden of medical expenses on a cancer patient, his/her relatives and the society is incomparable with other disease. So the related medical staffs are required to have a
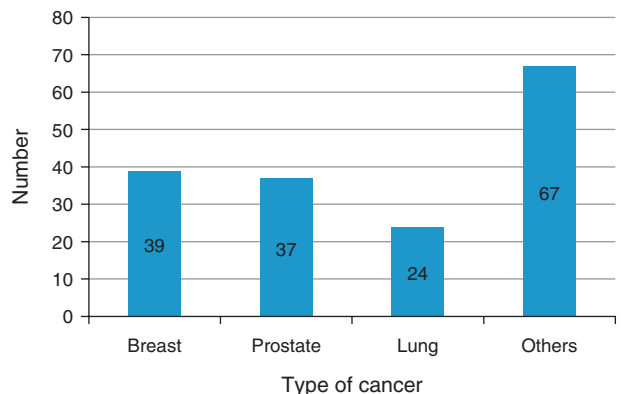

FIGURE 1. Frequency of type of primary malignant neoplasm in patients with bone metastases
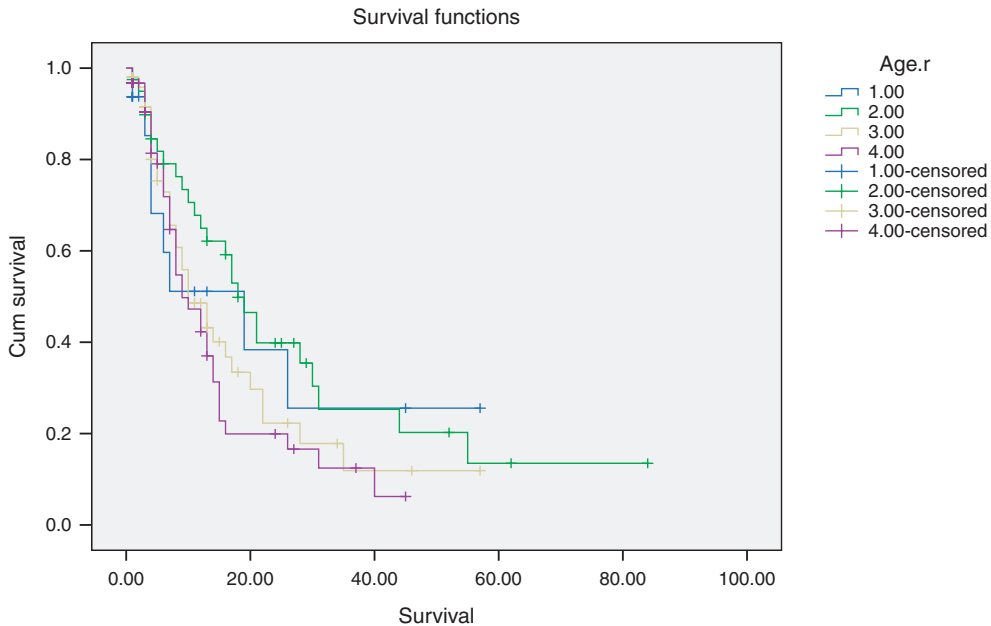
FIGURE 2. Overall survival in patients with bone metastasis according to age.

comprehensive knowledge about demographic, clinical, and pathological characteristics of cancer patients in order to take through the basic steps of planning for diagnosis, treatment, and rehabilitation processes. Therefore, according to the high prevalence of bone metastasis, particularly in breast, prostate, and lung cancers, and according to the importance of early detection of patients at risk, demographic, and clinicopathological characteristics and survival of patients with bone metastasis, who referred to Shahid Ramezanzadeh radiation oncology center in Yazd, Iran between 2007 and 2012, were examined in this study. In the current study, the prevalence of bone metastasis in males was a little more than that in females though it was not considerable. This study also indicated that most patients with bone metastasis were older than 66 years old. Kim et al[8] Conducted a study in Korea; 84 patients with bone metastasis of unknown primary cancer were selected; they consisted of 56 men and 28 women; a mean age of 59.1 years was reported. The results of the current study brought out some similarities to the results of above-mentioned research. In the current study, the frequency of cancer types was also evaluated, with the result that breast, prostate, and lung cancers were the most common cancer types in patients with bone metastasis. Bollen et al[9]
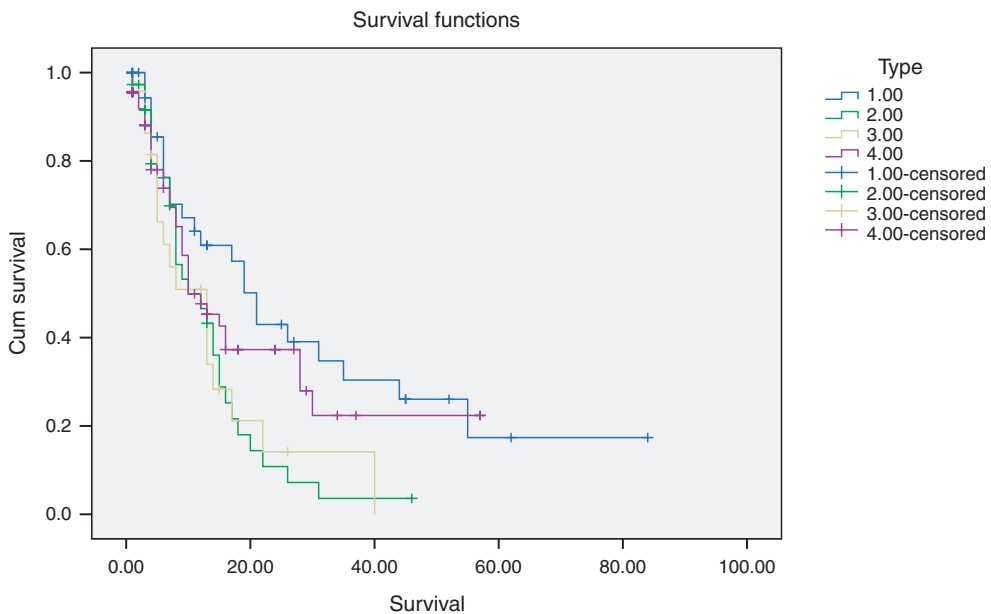

FIGURE 3. Overall survival in patients with bone metastasis according to type of cancer.
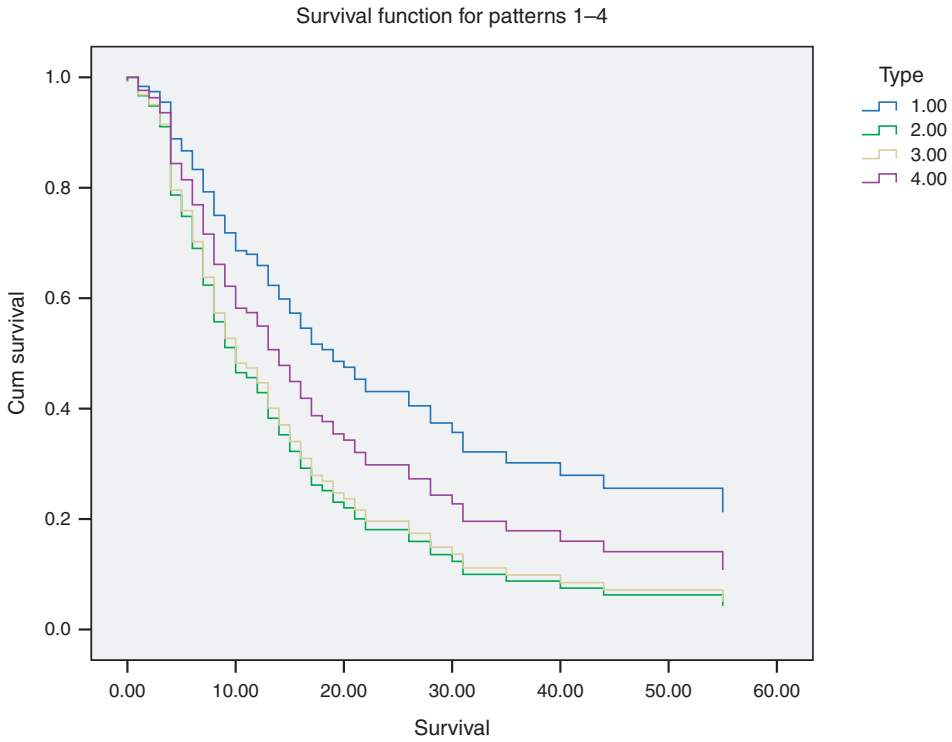
Survival function for patterns 1–4

FIGURE 4. Overall survival in patients with bone metastasis according to the type of cancer (taking account of age).

revealed that of 1043 patients with bone metastasis, 299 patients suffered from breast cancer, 250 patients were with lung cancer, and 215 patients suffered from prostate cancer. In a research by

Chen et al.[10] In the UK, the most common solid tumors, which led to bone metastasis, were breast, lung, prostate, thyroid, and renal carcinomas. Moreover, Kassa et al[11] in a prospective study
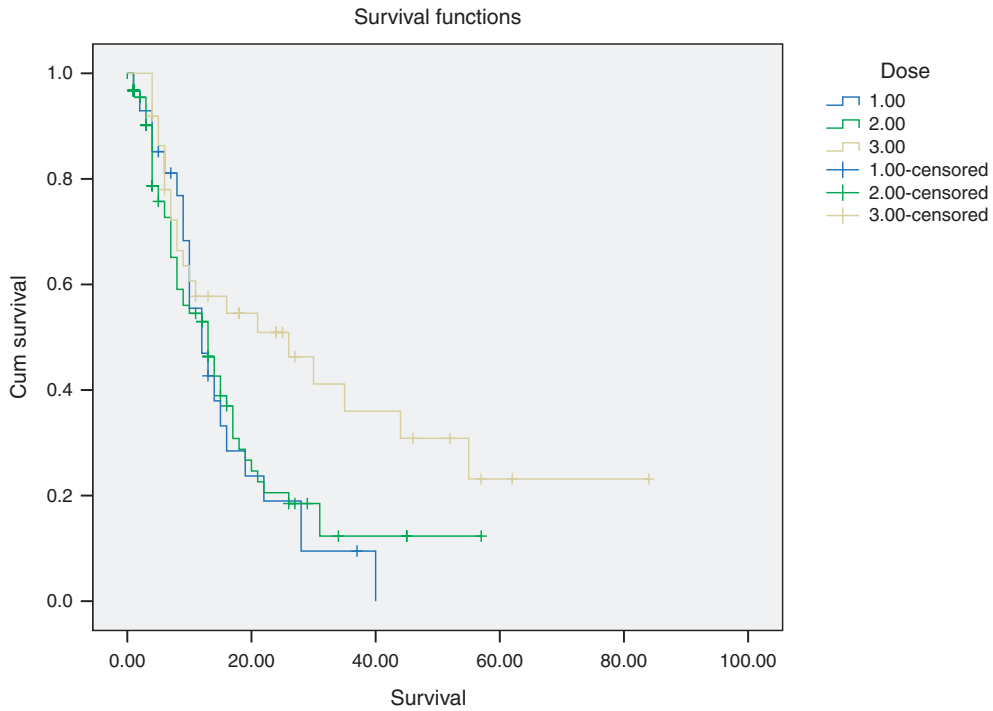
Survival functions

FIGURE 5. Overall survival in patients with bone metastasis according to radiation dosage.

reported that in 376 patients, who had been recruited, 38% were found with prostate cancer, 30% were determined to be breast cancer patients, and 11% had lung cancer, respectively. Considering previous studies, three most common cancers, which metastasize to bones are breast, prostate, and lung. The order of these cancers is different because of certain confounding variables such as the difference in the dominant sex of the target population and the environmental factors (cigarette, air pollution, and others). In the present study the initial manifestation of the disease in most patients was pain and it was neurologic complication and pathologic fracture in a few patients. The study by Farrel[12] also reported that pain was the most common manifestation of bone metastasis, which is compatible with the results of this study. The current study demonstrated that the disease was diagnosed by isotope bone scan in most patients and the diagnosis was made by MRI in certain patients. Rybak and Rosenthal[13] stated that although there are various procedures and the process of MRI is fast, isotope bone scan plays the most significant role in the diagnosis of bone metastasis. And this is also compatible with the results of the current study. In this study the evaluation of survival rate in patients with bone metastasis, showed that more than half of these patients died in the years between 2007 and 2012 and the other half survived or had an unknown state. The survival rate for patients with breast cancer was the highest (31.1 months) compared with other cancers; lung cancer and prostate cancer ranked second and third, in order. We should make it clear that there is no uro-oncologist in our province and patients with urologic malignancies are managed inadequately. Therefore, we think metastatic prostate cancers were diagnosed (by using isotope scan and/or cross sectional imaging) very late and because in this study the initial point for calculating overall survival was just at the time of diagnosis of bone metastasis, it is not surprising that these patients had a lower survival period than patients with lung cancer.

In a retrospective study completed by Domchek et al,[14] 718 women who referred to Massachusetts Hospital between 1981 and 1991 and diagnosed with metastatic breast carcinoma, greater than 50% of those with breast cancer developed skeletal complications and 37% of those were diagnosed with bone metastasis. Mean survival in group with bone metastasis was reported 26 months. And in a study by Farrel[12] mean survival in breast cancer patients with bone metastasis was also reported 24 months. Sugiura et al[15] conducted a study on *predictors of survival in patients with bone metastasis of lung cancer* in 2008 in Japan. They assessed survival rate for 118 patients. Mean survival was reported 9.7 months. In a study by Rief et al[16] in Germany, 303 patients with 868 osteolytic metastases who were treated with radiotherapy between 2000 and 2012 were examined. Overall survival at 6 months was 76.7% and it was 47.2% in 12 months. In a study carried out in 2008 by Chen et al.[10] It was shown that the mean survival of patients was 38.4 months, which was longer than that in western men and similar to that in Japanese men. The reason for the difference in survival of breast, lung and prostate cancer patients, in previous studies and the current study, can be dependent on patients' different ethnic groups, at what age the disease is diagnosed and the radiation dose that they received. Overall factors maybe contribute to racial disparities in mortality include differences in exposure to underlying risk factors and access to high-quality and timely diagnosis and treatment. In this study, the anatomic area which is involved with bone metastasis was also evaluated and the results showed that the metastasis in most patients involved lumbar vertebrae. The evaluation of common cancers

in men and women with bone metastases also demonstrated that prostate, lung, and gastrointestinal cancers in men, and breast, gastrointestinal, and lung cancers in women were the most prevalent. Jemal et al[17] in a research on *Cancer Statics* in 2005 in America estimated that the most commonly diagnosed cancers among men were prostate, lung, and colon. The most common cancers among women were cancers of breast, lung, and colon. The results of the current study support this research results. In addition, in the present study, the correlation between the life status in patients, and various demographic variables (age, sex, type of cancer, the amount of radiation dose absorbed in the first visit, the initial manifestation of the disease, and involved anatomic area) were assessed. Our study was not designed to investigate the relationship between survival and systemic treatments. Based on the obtained results of Log-rank test, there was only a meaningful correlation between demographic variables – sex, type of cancer and radiation dose – and the life status in patients. In this study, the correlation between the type of cancer and patients survival was also calculated using Cox Regression test based on the age of the patients. Without considering the age, prostate and lung cancers increased the risk of death compared with breast cancer. Since we added the age variable to this study, type of cancer lost its effect, and there was no significant difference between prostate cancer and lung cancer compared with breast cancer. When we adjusted the effect of age, we found that the age variable was more effective than the variable of cancer type in survival of patients with bone metastasis who had referred to this oncology center.

CONCLUSION

In conclusion, the patients referred to this center while they were complaining of pain as the first symptom of the disease and their lumbar vertebrae were involved more than the other parts of the body. The mortality rate was high in these patients and it equated with more than half of the patients with bone metastasis. Great numbers of men who referred to this oncology center were found to be prostate cancer patients and the breast cancer was the most frequent in women with bone metastasis, considering this fact that most of these patients were diagnosed by radioisotope bone scan. According to the results of this study, it seems that for increasing the survival of patients, who are at high risk for cancer, particularly the patients with a history of certain cancers such as prostate and breast in the family, it is required to widely use the screening strategies. The information should be publicly available and people and physicians should be aware of the necessity of screening tests. In addition patients with bone metastasis should be referred to medical centers that have a multidisciplinary team of cancer specialists with experience treating them. Considering these points enable us to provide early diagnosis of the disease and improve the quality of life in patients.

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