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Letter to Editor

# Is it necessary to do surgical fixation in metastatic bone disease impending pathologic fracture before $^{177}$Lu-prostate-specific membrane antigen radionuclide therapy?

Current advance in treatment options of patients with prostate cancer has improved the mean survival of patients with disseminated disease. Recently, Lu-prostate-specific membrane antigen (PSMA) radionuclide therapy as a ubiquitous molecular radiotherapy approach is considered an effective treatment in patients with metastatic castration-resistant prostate cancer.[1]

However, most candidate patients have metastatic bone lesions predisposing the bone to an impending fracture. The pathologic fractures are sometimes seen following Lu-PSMA radionuclide therapy, even after one cycle, in the spine, pelvis, and extremities. As a fact, hormonal ablation as the principal treatment partly predisposes the patients to bone loss in prostate cancer.[2]

A pathologic fracture during molecular radiotherapy using Lu-PSMA would expose the patients to devastating pain, immediate hospitalization, and surgical intervention in the situation that are not ideal. Hence, forecasting an impending fracture and preventive fixation before Lu-PSMA radionuclide therapy are vital to minimize debilitating complications.

Actually, there are no comprehensive reports on this issue but few studies presented as a side effects through clinical outcome assessment following $^{177}$Lu-PSMA therapy. In a prospective pilot study in 21 Asian populations with advanced prostate cancer taking $^{177}$Lu-PSMA, two patients had pathological hip and humeral fractures.[3]

The key question is whether it is necessary to fix the bony lesions before Lu-PSMA radionuclide therapy.

In this regard, a number of studies were conducted to determine the features of an impending pathologic fracture. Mirels suggested a practical, reproducible, and accurate rating system protocol to categorize the risk of pathologic fracture that could serve a basis for decision-making regarding prophylactic fixation in metastatic diseases in long bones before using drugs or radiotherapy.[4]

Mirels' classification predicts the highest risk of pathological fracture among metastatic diseases in long bones based on the site, nature, size, and pain. All of the parameters are scored from 1 to 3.

The lesion site is divided into three parts including upper extremity, lower extremity, and peritrochanteric area of the femur, and scored from 1 to 3, respectively. In general, it is seen that those lesions in the peritrochanteric area are at high risk for fracture; moreover, the chance of pathologic fractures is higher for weight-bearing skeleton compared to nonweight-bearing bones. The nature or matrix of the lesion is also subclassified into three parts (scored from 1 to 3) including blastic, mixed, and lytic, and the chance of fracture in three categories is 0%, 32%, and 48%, respectively.[4]

The lesion size is presented as a proportion of the cortical thickness. A score of 1, 2, and 3 is given to lesions/cortex ratios of $<1.3$, 1.3–2.3, and $>2.3$, respectively. The frequency of pathologic fracture is 0% for lesions $<1.3$ of the cortex, 5% for lesions between 1.3 and 2.3 of the cortex, and 81% for lesions involving $>2.3$ of the cortex.[4]

The only subjective parameter in Mirels' criteria is pain in which mild, moderate, or functional pain received a score of 1, 2, and 3, respectively. The frequency of fracture is only 10% in patients with mild-to-moderate pain in contrast to progression of fracture in patients with functional pain. Moreover, there is a relationship between pain and the lesion size.[4]

According to the overall score, a recommendation is proposed regarding prophylactic fixation of the lesion. Based on the Mirels' classification, preventive fixation is strongly recommended for a lesion with a total score of 9 or higher.[4] A lesion with a total score of 7 or less can be treated with radiotherapy and drugs without concerns. A total score of 8 presents a clinical dilemma; however, Mirels proposed that clinicians use clinical appraisal in such situations and conduct prophylactic fixation.[4]

The overall sensitivity and specificity of the Mirels' protocol for predicting fracture are 91% and 35%, respectively, which may cause a substantial degree of overtreatment; nevertheless, once a pathologic fracture occurs, the consequences are even more serious.[5]

As mentioned earlier, the Mirels' system is only appropriate for metastatic lesions in long bones and cannot be used in the spine and presumably oncological management is discussed in the spine separately from nonspine metastases.[6] The spine is frequently affected by prostate cancer and could be assessed by an alternative noninvasive approach proposed by Snyder *et al*.[7] What's more, Fisher *et al*. presented a unique classification model for spinal instability in metastatic disease.[8]

The Spine Instability Neoplastic Score is a holistic approach that can help clinicians in ascertaining when cases with malignant disease of the spine may advantage from surgical consultation. It includes pain, spinal alignment, global spinal location of tumor, bone lesion quality, posterior involvement, and vertebral body collapse. It also could be helpful for surgical decision-making when take account with other key parameters such as neurologic symptoms, disease extension, prognosis, patient health elements, types of tumors, and tumor radiosensitivity.[8]

It needs to be emphasized that a few important issues should be considered to make an informed decision.

The Mirels' score was validated in patients with bone metastases to the appendicular skeleton who were evaluated with radiographs and subsequently treated with external beam radiotherapy. This patient population presents starkly different characteristics from prostate cancer patients treated with Lu-177 PSMA radioligand therapy in the following ways:

1. Initial assessment is done more commonly with Ga-68 PSMA positron emission tomography/computed tomography (CT). The CT component of this hybrid imaging has a significantly different performance than radiographs
2. Prostate cancer metastases occur first to the more richly vascularized axial skeleton compared with the appendicular skeletal metastases on which the Mirels' score was validated.
3. Mirels' cohort was treated with external beam radiotherapy. The dense energy impacted within a short period of time in radiotherapy contrast with the longer duration of irradiation of cancer cells and surrounding bone tissue in radionuclide therapy.

There are some unanswered points in this challenging issue. First, the method of calculating the total score is not clear in patients with multiple metastases of varying sizes in different locations with different levels of pain intensity, which are commonly seen in the patients referred for Lu-PSMA radionuclide therapy, the method overall score calculation is unknown. Second, there is a relationship between the histology of the primary lesion and fracture, which is not considered in the Mirels' classification. Third, in addition to four included parameters in this system, several other factors should be assessed as predictors of fracture, including previous treatments, comorbidities, estimated period of survival, other disease sites, level of activity, and bone mineral density, which are not addressed in this classification system.

The Mirels' classification system for impending pathologic fracture could be a reasonable approach for prostate cancer patients with metastases in long bones referred for Lu-PSMA radionuclide therapy until further specific valid methods are developed in this regard. However, there is still room for developing a more specific system for radionuclide therapy in bone metastases. In addition, given widespread use of Lu-PSMA radionuclide therapy in prostate cancer patients, it seems necessary to take appropriate measures to maintain and promote bone health in the patients referred for this therapy.

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## Conflicts of interest

There are no conflicts of interest.

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