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Detection of bone metastases in patients with cancer: 99mTc-MDP bone scan and 18F-FDG PET/CT.

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Abstract

99mTc-MDP bone scan has been the standard method for nuclear imaging of the skeletal system for decades, providing information about the presence, location, extent, and response to therapy in patients with bone metastasis. However, there are few improvements in radiopharmaceutical and gamma camera technology for 99mTc-MDP bone scan during the past decades, and the supply of 99mTc-MDP has become unstable because of the decrease in the number of active nuclear reactors in recent years. ^{18}F-FDG PET/CT has a proven role in staging and monitoring different cancers. However, much still remains unknown about the validity of ^{18}F-FDG PET/CT for the detection of malignant bone involvement. The aim of this study was to review the related literatures and compare the diagnostic efficacy of 99mTc-MDP bone scan and ^{18}F-FDG PET/CT in ruling out bone metastases. The respective advantages of the two techniques in detecting bone metastases from tumors of different positions and different types were summarized.

Keywords: 99Tc-MDP, ^{18}F-FDG, Positron emission tomography-computed tomography (PET/CT), Bone metastasis.

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General features of 99Tc-MDP and ^{18}F-FDG PET/CT

99m *Tc-MDP bone scan*

Technetium-99m, a bone-seeking tracer, is rapidly deposited to bones ,binds to bone crystal surface by chemiscorption after intravenous injection and shows bone metabolism specifically. Lesions in the bone, such as inflammation, primary bone tumors, bone metastases and fractures, will cause changes in local blood flow, bone mineral metabolism and increased radioactivity.

99mTc-MDP bone scintigraphy (BS) is highly sensitive and cost-effective and has been considered the primary choice for nuclear imaging of the skeletal system since the 1970s. The imaging technique plays an important role in preoperative evaluation, treatment efficacy evaluation and monitoring of bone metastases. Another advantage of bone scan is that it is a non-invasive technique for early diagnosis and localization of bone diseases. However, due to poor spatial resolution, blind spot, and extended duration of examination, the overall usefulness is limited to some extent. The specificity is low. The sensitivity is highly related with anatomical localization of bone metastasis [1]. The sensitivity was only 40% for bone metastases in the spine and pelvis. However, the sensitivity was up to 83% for bone metastasis in skull, ribs and extremities [1]. In addition, the uptake of the imaging agents for the diagnosis of bone metastases also depends on the response of osteoblasts and the accompanying increase of local blood flow in tumor cells [2]. Therefore, imaging method of bone scan based on reactive osteoblastic changes may result in false negative result for those bone metastases featuring predominantly bone destruction but lacking in activity of osteoblasts.

^{18}*F-FDG PET/CT*

^{18}F-FDG PET/CT is a well-known functional imaging modality in oncology areas. With the continuous promotion in clinical practice, the role of ^{18}F-FDG PET/CT in tumor diagnosis, staging and detection has been affirmed by clinicians. It has higher spatial resolution and combines nuclear imaging with ordinary CT scan. The uptake mechanism of the radiopharmaceutical in bone metastases depends on the pathological increase in glycolytic activity of the malignant cells; therefore ^{18}F-FDG shows specifically the malignancy of the bone [1]. The application of ^{18}F-FDG PET/CT imaging can avoid false-positive results caused by many benign bone diseases. ^{18}F-FDG PET/CT is also considered increasingly important in the diagnosis of bone metastases from cancers. Its clinical role in diagnosing bone involvement is gaining recognition [3,4] .

Comparison of diagnostic efficiency in bone metastases from different cancers

Considering the advantage and disadvantage of 99Tc-MDP BS and ^{18}F-FDG PET/CT, more and more studies focused on the diagnostic value of these two methods in bone metastases in different cancers. However, most of studies just focus on one type of cancers of bone metastasis. We will review these literatures and try to figure out the most appropriate imaging method for those patients that develop bone metastases from different cancers.

Comparison of diagnostic efficiency in bone metastases from lung cancer

Lung cancer has become one of the most common cancers in China with increasing incidence. Bone is good hair parts of the lung cancer metastasis. At present, bone scan is still a common method for clinical diagnosis of bone metastases from lung cancer. With wide applications of PET/CT in recent years, the diagnostic efficacy of bone metastases has gained more attention. Xu Weina et al. [5] reviewed 49 cases of lung cancer patients with bone metastases, including 18 cases of squamous cell carcinoma, 23 cases of adenocarcinoma, 2 cases of small cell lung cancer, 5 cases of adenosquamous carcinoma and 1 case of bronchioloalveolar carcinoma. The results indicated that the sensitivities of ^{18}F-FDG PET/CT and bone scan in the diagnosis of bone metastases from lung cancer were 90.8% and 56.6%, and the specificities were 93.5% and 45.2%, respectively. In their study, osteolytic bone metastasis was the predominant type of bone metastases, a few cases had osteogenic bone metastases, and some cases were of the mixed type. Therefore, the diagnostic sensitivity and accuracy of ^{18}F-FDG PET/CT in bone metastases from lung cancer are higher than that of bone scan. But bone scan has obvious advantages in detecting osteogenic bone metastases.

Qu x et al. also made a Meta-analysis on the diagnostic value of ^{18}F-PET/CT, PET, MRI and bone scan on bone metastases from lung cancers [6]. By preliminary research, 1670 studies were found and 17 of them (2940 patients) were finally included. It was found that the diagnostic sensitivity of ^{18}F-FDG PET/CT, ^{18}F-FDG PET, MRI and bone scan in bone metastases from lung cancer was 92.0%, 87.0%, 77.0% and 86.0%, respectively; The overall specificity was 98.0%, 94.0%, 92.0% and 88.0%, respectively. Thus ^{18}F-FDG PET/CT had the highest diagnostic value in bone metastases from lung cancer, while MRI had the highest specificity but lower sensitivity; Bone scan was least costly and had moderate sensitivity and specificity.

During the same period, a meta-analysis in Acad Radiol searched for related literatures from 1995 to 2010 and compared the diagnostic accuracy of ^{18}F-FDG PET, ^{18}F-FDG PET/CT and bone scan in bone metastases from lung cancer. It was concluded that either ^{18}F-FDG PET or ^{18}F-FDG PET/CT had higher diagnostic sensitivity and specificity than bone scan for bone metastases from lung cancer [7].

With application of meta-analysis, Cheng Xu compared ^{18}F-FDG PET/CT and 99mTc-MDP bone scan by reviewing relevant English literatures from 2000 to 2010 [8]. A preliminary search produced 255 articles related to the topic, and 6 studies conformed to all the inclusion and exclusion criteria. The selected studies covered all types of cancers: non-small cell lung cancer (1341 cases), small cell lung cancer (14 cases), nasopharyngeal carcinoma (111 cases), Ewing sarcoma (111 cases), rhabdomyoma sarcomatosum (5 cases), neuroblastoma (8 cases) and ganglioneuroblastoma (1 case). The meta-analysis showed that for ^{18}F-FDG PET/CTthe sensitivity was 93.4%, specificity 95.7%, positive likelihood ratio 34.990, negative likelihood ratio 0.068, diagnostic odds ratio 559.02 and the area under the curve (AUC) 0.9854; For bone scan, the sensitivity was 0.706, specificity 0.911, positive likelihood ratio 13.982, negative likelihood ratio 0.319, diagnostic odds ratio 60.420, and AUC 0.9386 (Table 1).

These studies showed that that ^{18}F-FDG PET/CT had a higher diagnostic sensitivity and specificity than bone scan on bone metastases from lung cancers.

Table 1. *Meta-analysis of 6 studies.*

	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio	The area under the curve
18F-FDG PET/CT	93.40%	95.70%	34.99	0.068	559.02	0.985
Bone scan	70.60%	91.10%	13.98	0.319	60.42	0.939

Comparison of diagnostic efficiency in bone metastases from small cell lung cancer (SCLC)

SCLC is the most aggressive form of lung cancer, accounting for 15-20%. If the tumor is confined to one side of the chest (with the involvement of regional lymph nodes, such as hilar lymph nodes, mediastinal lymph nodes and supraclavicular lymph nodes) and can be incorporated into one radiotherapy field, it is defined as limited disease (LD); otherwise it is extensive disease (ED) [9]. At present, for most patients with LD, chemotherapy combined with chest radiotherapy is the common therapy, and the patients with ED usually receive combination chemotherapy [10]. Since the treatment for LD and ED is different, accurate staging is essential. Chest and abdominal CT, brain CT or MRI, and bone scan are recommended as routine diagnostic tests [11].

Bone marrow is the most common site of metastasis for SCLC. Bone marrow metastases are considered the sources of bone metastases in SCLC. A study showed that approximately 20% of SCLC patients had bone marrow infiltration, as demonstrated by bone marrow biopsy. Moreover, almost all of the SCLC-related bone metastases originated from the bone marrow [12]. Another study showed that 48% of bone marrow lesions in 100 SCLC patients turned into focal concentrated sites during the follow-up period of 57-154 days according to

bone scan. Moreover, 88% of the new lesions found by bone scan were developed from the adjacent bone marrow lesions. This study also showed that 64% of false-negative lesions (21/33) developed into new lesions in the follow-up bone scan.

The most common site of metastasis for SCLC upon initial diagnosis is bone and bone marrow. Autopsy data indicate that 45-54% of bone or bone marrow metastases were seen in SCLC patients [10,13,14]. Therefore, it is important to assess bone or bone marrow metastases for primary clinical staging.

Lee et al. [15] compared the diagnostic accuracy of ^{18}F-FDG PET/CT and bone scan in SCLC, and evaluated whether ^{18}F-FDG PET/CT could be used instead of bone scan for the staging. The results showed that in 84 metastatic bone lesions, the lesions found positive by ^{18}F-FDG PET/CT, but missed by bone scan accounted for 61%. ^{18}F-FDG PET/CT missed only 2% of the metastatic bone lesions, which were outside of the scan field of view. By the follow-up bone scan, 21 lesions were detected, and these lesions were already found in the initial ^{18}F-FDG PET/CT.

^{18}F-FDG PET/CT improves the accuracy of SCLC staging and benefits to the clinical decision-making. Although bone scan has a larger scan range than ^{18}F-FDG PET/CT and provides whole-body views, ^{18}F-FDG PET/CT can be used to replace bone scan for early clinical staging of SCLC. Moreover, ^{18}F-FDG PET/CT provides precise anatomic localization and better discriminates between bone metastasis, fracture and degenerative diseases, which helps reduce false-positive diagnosis.

Koolen et al. [16] reported some FDG-avid sclerotic bone metastases and pointed out that the invasiveness of the tumor affected the uptake of ^{18}F-FDG in bone metastases more greatly than the metabolic characteristics of bone metastases did. SCLC-related bone metastases were usually high in the metabolism of ^{18}F-FDG, which was typical of aggressive tumors and usually associated with osteolytic bone metastases. Most of the bone metastases in SCLC are derived from bone marrow. Therefore, ^{18}F-FDG PET/CT is superior to bone scan in the detection of bone metastases from SCLC. If ^{18}F-FDG PET/CT is already applied for the staging of SCLC, there is no more need to perform bone scan.

Comparison of diagnostic efficiency in bone metastases from differentiated thyroid carcinoma (DTC)

Besides lung, bone is also the common site of distant metastases for DTC. Non-invasive imaging methods are useful for early detection of bone metastases and follow-up of DTC, including CT, MRI, BS, ^{131}I-WBS, ^{131}I-SPECT/CT and ^{18}F-FDG-PET/CT. Imaging plays an important role in formulating the treatment scheme and predicting prognosis. In the current clinical studies, bone scan has been widely used in the diagnosis of bone metastases from a variety of cancers as a very cost-efficient tool. However, it was reported [17,18] that due to the lack of osteoblast response, bone scan was more likely to make false-negative diagnosis of osteolytic bone metastases. ^{131}I-SPECT/CT can provide metabolic and anatomic information of the lesions, so it is easier to locate the lesions and confirm the result of ^{131}I-WBS [19]. ^{18}F-FDG PET/CT can also confirm the recurrence or metastasis of DTC, and it is mainly used to ascertain whether there were metastases in patients with negative ^{131}I-WBS result and elevated serum Tg [20,21].

Qiu ZL analyzed the diagnostic and prognostic value of bone scan, ^{131}I-SPECT/CT and ^{18}F-FDG PET/CT in bone metastases from DTC [22]. They found that in the diagnosis of bone metastases from DTC, ^{131}I-SPECT/CT and ^{18}F-FDG PET/CT were better than bone scan. ^{131}I-SPECT/CT combined with ^{18}F-FDG PET/CT was accurate in the diagnosis of nearly all patients with bone metastases from DTC. Bone scan might be completely replaced by ^{131}I-SPECT/CT and ^{18}F-FDG PET/CT. In addition, the survival time of patients with positive ^{18}F-FDG PET/CT result was significantly shorter than that of patients with negative ^{18}F-FDG PET/CT result. Multivariate analysis showed that suspected bone metastases combined with other distant metastases and positive PET were independent factors of poor prognosis. Patients with positive results of PET had an increase of death risk by 7.28 times.

Comparison of diagnostic efficiency in bone metastases from other cancers

Ozülker et al. [23] compared ^{18}F-FDG-PET/CT with ^{99m}Tc-MDP bone scan in the detection of bone metastases from cancers in 2010. Seventy cases of various cancers were retrospectively analyzed, including 39 cases of mammary cancer, 7 cases of unknown primary lesions, 5 cases of lung cancer, 3 cases of nasopharyngeal carcinoma, 2 cases of NHL, 2 cases of rectal cancer, 2 cases of prostate cancer, 1 case of lung cancer combined with breast cancer, 1 case of breast cancer combined with ovarian cancer, 1 case of thyroid cancer combined with prostate cancer, 1 case of pancreatic cancer, 1 case of bladder cancer, 1 case of gastric cancer, 1 case of renal carcinoma, 1 case of liver cancer, 1 case of laryngeal carcinoma and 1 case of malignant mesenchymal tumor. ^{18}F-FDG PET/CT found bone metastases in 68 cases, and the diagnostic sensitivity was 97.1%; 2 cases of missed diagnosis were sclerotic bone metastases from lung cancer combined with breast cancer, which were not identified by PET, but by CT scan. Bone scan found bone metastases in 60 cases, and the diagnostic sensitivity was 85.7%. Cases of missed diagnosis were 6 cases of breast cancer, 1 case of unknown primary lesion, 1 case of lung cancer, 1 case of laryngeal cancer and 1 case of bone metastases from malignant mesenchymal tumors. ^{18}F-FDG PET/CT correctly diagnosed 38 cases of breast cancer (97.4%), and bone scan 33 cases (84.6%). Among 10 cases, ^{18}F-FDG PET/CT discovered more metastatic lesions than bone scan did. ^{18}F-FDG PET/CT showed that 31 cases had organ metastases, while 7 cases with unknown primary lesions were found to have primary foci. ^{18}F-FDG PET/CT found 1 case with bone metastases among 2 cases with prostate cancer, and the number of lesions was less than that found by bone scan. So this meta-analysis concluded that in the

diagnosis of bone metastases, ^{18}F-FDG PET/CT is more sensitive than bone scan except for bone metastases from prostate cancer. In addition to the diagnosis of bone metastases, ^{18}F-FDG PET/CT was also superior in diagnosing primary tumors and displaying organ metastases. In their study, the spine rich in red marrow was the most commonly affected. The tumor cells first occur in the red marrow in bone metastases, and this explains why bone metastases occur more frequently in the spine. The diagnosis of spinal metastases by ^{18}F-FDG PET/CT was more accurate than bone scan. This conclusion was consistent with the results by domestic scholar Wang et al [24].

The diagnostic efficiency in bone metastases from breast cancers was also proved by another study. Sixty-two patients with breast cancers received both 18F-FDG-PET/CT and BS. The sensitivity and specificity for 18F-FDG-PET/CT were higher than BS in the screening of metastatic bone lesions in all patients [25]. Al-Bulushi et al. also analyzed 319 patients with head and neck cancer and found that F-FDG PET/CT was superior to Tc-methylene diphosphonate bone scan in detecting bone metastases in head and neck cancer [26] Another study also found that 18F-FDG PET/CT achieved higher sensitivity, specificity, and accuracy in detecting osteolytic bone metastases than 99mTc-MDP whole-body BS , suggesting F-FDG PET/CT has also a higher diagnostic value than (99m)Tc-MDP whole-body BS in the detection of osteolytic bone metastases, especially in the vertebra [27].

Cook et al. reported that ^{18}F-FDG PET was superior to bone scan in the diagnosis of bone involvement from breast cancer, and the positive result of ^{18}F-FDG PET usually indicated poor prognosis [28]. However, for osteoblastic bone metastases, due to low metabolic rate, ^{18}F-FDG PET was often not as sensitive as bone scan. Sclerotic bone metastases were more easily detected by CT. Therefore, CT can make up for the defects of ^{18}F-FDG PET/CT in the diagnosis of bone metastases. It was inferred that the non-uptake of ^{18}F-FDG in the skeletal lesions may be secondary to osteogenesis, which was commonly seen in osteolytic bone metastases after successful treatment. However, this hypothesis is not always correct. With the progression of osteoblastic metastases, CT would display enlarged nodules, probably in the absence of significant uptake of FDG. Sahin E et al. suggested that for the detection of bone metastases the specificity and accuracy of ^{18}F-FDG-PET/CT were higher compared to BS, while the sensitivity was lower. Both studies are complementary to final diagnosis [29].

In the diagnosis of osteosarcoma, PET/CT is more sensitive and accurate than BS for diagnosing bone metastases. The combined use of PET/CT and BS improves sensitivity [30]. ^{18}F-fluoride PET/CT has higher sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in detecting bone metastases in urinary bladder carcinoma than conventional (99m)Tc-MDP planar BS. SPECT/CT improves all these parameters compared with planar BS and may serve as a cost-effective screening procedure for the detection of skeletal metastases in high-risk patients [31].

The primary site of bone metastases is usually bone marrow rather than bone. When the lesion was confined to the bone marrow, it was usually detected earlier by ^{18}F-FDG PET/CT than by bone scan. [28] However, bone scan provides indirect evidence of reactive bone formation after long-term infiltration of the lesions in red marrow. In addition, the main site of bone metastases is also bone marrow, and the activity of the lesions is most important for the evaluation of response to treatment. Bone scan may show positive result in responsiveness evaluation for quite a long time, because osteogenesis secondary to bone marrow lesions will continue for a long time after successful treatment [32].

Prospect

The uptake of 99mTc-MDP mainly reflects the activity of osteoblasts. Bone scan is more effective in the detection of bone metastases from breast cancer, prostate cancer and lung cancer, from which the bone metastases are mostly osteoblastic bone metastases. Therefore, bone scan is less accurate in the diagnosis of osteolytic bone metastases without or with very small degree of osteogenesis, such as myeloma, renal cell carcinoma, thyroid cancer and aggressive metastases with rapid bone damage (eg, SCLC). The diagnostic sensitivity of ^{18}F-FDG PET/CT is high for osteolytic bone metastases, and its overall diagnostic efficiency is significantly higher than that of bone scan. When it comes to sclerotic bone metastasis, CT scan can make up for the defects of PET in PET/CT.

The reasons of false-positive diagnosis by bone scan mainly include degenerative bone diseases, fractures, trauma and inflammation. Compared with bone scan, ^{18}F-FDP PET/CT is seldom affected by nonspecific uptake in the benign bone lesions. A diagnosis is much easier and more accurate by combining radionuclide imaging of metabolism and anatomical localization by CT scan in ^{18}F-FDP PET/CT. For example, bone fractures more than 2-3 months old are usually negative in PET and they are easier to diagnose in combination with CT images. For a long time, bone scan will indicate abnormal concentration at the site of bone fracture until the bone fracture is completely healed with functional recovery [3]. Therefore, bone fracture is one of the most common causes of false-positive result in bone scan.

For bone metastases from cancers, ^{18}F-FDP PET/CT has higher diagnostic sensitivity and specificity than bone scan and can be used as an alternative to bone scan. ^{18}F-FDP PET/CT can be also used to discover primary tumors and organ metastases. ^{18}F-FDP PET/CT is a useful complement for bone scan in cancers, especially osteogenic bone metastases, such as prostate cancer and breast cancer.

For DTC, ^{18}F-FDP PET/CT can be applied to patients with negative ^{131}I-WBS result and elevated serum Tg. In addition, positive result of ^{18}F-FDP PET usually indicates poor prognosis in DTC patients with bone metastases.

Many studies have indicated that ^{18}F-FDGPET/CT has higher diagnostic sensitivity and specificity than bone scan in bone metastases from cancers. However, further researches are

needed to evaluate the diagnostic efficacy of the two in bone metastases from different pathological types of cancers. Only with a good knowledge of respective diagnostic advantages of ^{18}F-FDGPET/CT and bone scan in bone metastases from each type of cancer can clinicians select the most appropriate imaging technique according to the location and pathological type of primary cancers.

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