Research Highlights

Highlights from the latest articles in bone imaging: new insights from research with CT, MRI and PET

PET-CT in an osteoporosis animal model

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Evaluation of: Cheng C, Heiss C, Dimitrakopoulou-Strauss A *et al.* Evaluation of bone remodeling with (18)F-fluoride and correlation with the glucose metabolism measured by (18)F-FDG in lumbar spine with time in an experimental nude rat model with osteoporosis using dynamic PET-CT. *Am. J. Nucl. Med. Mol. Imaging* 3(2), 118–128 (2013).

Bone pathology and diagnosis were among the first to benefit from modern methods of imaging. As the bone is among the most common tissues where malignant tumors metastasize, but is also subjected to a multitude of non-neoplastic diseases, such as osteonecrosis, developmental abnormalities, osteomyelitis cystic and metabolic disease, research in the field of bone imaging is continuing and gaining new dimensions, as increasingly powerful techniques are combined.

One of the newest and most original approaches published during the last few months is an evaluation method for bone remodeling using PET-CT on rats with an experimental osteoporosis model. Caixia *et al.* used an animal osteoporosis model and PET evaluation of ^{18}F-fludeoxyglucose (^{18}F-FDG) glucose metabolism for assessing the risk of bone mineral density loss [1].

There are several methods of measuring bone mineral density among which are dual-energy-ray absorptiometry, high-resolution peripheral CT and ultrasonic densitometry. However, PET using ^{18}F-FDG has an advantage in the fact that fluoride ion enters bone metabolism as one of its normal components, as it enters into the hydroxyapatite crystals of the bone to form fluoroapatite, which is deposited mostly in the wear surfaces of the bone, close to the joints, where bone turnover is most important.

PET was employed to follow the evolution of fluoride in the bones of normal and osteoporotic female rats, while data using ^{18}F-FDG were used to estimate bone metabolism from glucose consumption. The osteoporosis model in rats was obtained by feeding a low-calcium, low-D2/D3 diet to ovariectomized rats, with or without the addition of dexamethazone. The degree of osteoporosis was estimated by dynamic PET-CT.

The dynamic PET studies for both ^{18}F and ^{18}F-FDG were performed using a 28-frame protocol for l h. The images were then superimposed over a ultra-high CT scan and reconstructed to standardized uptake value using a proprietary software. Evaluation of plasma clearance of tracer to bone mineral was made using a two-compartment model. ^{18}F serves as a marker of bone blood flow and of osteoblast activity, while ^{18}F-FDG follows the regional blood flow and the glucose metabolism. The study demonstrates the viability of the osteoporosis model in rats and also a lack of correlation between the standardized uptake values for glucose and fluorine, which seems to characterize osteoporosis. It seems that "…changes in bone remodeling and glucose metabolism may be different for each osteoporosis type…" [1].

The value of the study lies mainly in the methods devised for the evaluation and quantification of osteoporosis, bone fluoride deposition and bone metabolism.

References

1 Cheng C, Heiss C, Dimitrakopoulou-Strauss A *et al.* Evaluation of bone remodeling with (18)F-fluoride and correlation with the glucose metabolism measured by (18)F-FDG in lumbar spine with time in an experimental nude rat model with osteoporosis using dynamic PET-CT. *Am. J. Nucl. Med. Mol. Imaging* 3(2), 118–128 (2013).

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Future Medicine part of fsg

Value of multimodal MR and PET imaging in small animals

Evaluation of: Doré-Savard L, Barrière DA, Midavaine E *et al.* Mammary cancer bone metastasis follow-up using multimodal small-animal MR and PET imaging. *J. Nucl. Med.* 54(6), 944–952 (2013).

This is a brilliant use of a combination of PET imaging and MRI in following the evolution of bone metastases of breast cancer using a rat model [1]. The theme chosen by the authors is very well thought out, as breast cancer is one of the most common malignancies of the decade and the ability of curing it is severely hampered by metastases, which occur in more than 70% of the cases. As breast cancer frequently metastasize in the bone, the only way of identifying and staging it is using imaging techniques such as scintigraphy, CT, MRI or PET.

The authors have experience in the field of animal models having already used ^{18}F-NaF PET to follow the evolution of bone metastases in animal models combined with gadolinium-enhanced T1-weighted MRI.

Rat carcinoma cells were injected in the medullar cavity of the femur of adult male Sprague–Dawley rats. During the 15 days following inoculation, the animals were imaged daily, then animals were euthanized and samples for micro-CT and histology were taken. MRI and PET scans were administered daily. For imaging purposes they also received ^{11}C-methionine (to evaluate the protein metabolism), ^{18}F-NaF (to evaluate bone metabolism) or ^{18}F-FDG (for the evaluation of the metabolic activity of the tumor site).

The paper describes, in detail, both the imagistic and histologic aspects of the evolution of the tumoral inoculum. Metabolic evolution of the tumor was closely followed by the functional PET using tagged methionine, sodium fluoride and FDG. The results demonstrated that ^{11}C-methionine-uptake was higher than ^{18}F-FDG, which was in accordance with the data in the literature, which showed that ^{11}C-methionine detects more metastases than classic PET with ^{18}F-FDG. Another valuable conclusion of this study was that manually drawn regions of interest are more precise in quantifying standardized uptake values than automatic, threshold-determined regions. The MR images were sufficient for reducing user variability when drawing the regions of interest.

This is a remarkable animal study, amply demonstrating the usefulness of animal studies in the diagnosis and follow-up of human pathology and the advantages of multimodal imaging approach. An extremely useful lecture both for clinicians and fundamental researchers.

Reference

1 Doré-Savard L, Barrière DA, Midavaine E *et al.* Mammary cancer bone metastasis follow-up using multimodal small-animal MR and PET imaging. *J. Nucl. Med.* 54(6), 944–952 (2013).

PET and MRI in the diagnose of bone marrow lymphoma

Evaluation of: Adams HJ, Kwee TC, Vermoolen MA *et al.* Whole-body MRI for the detection of bone marrow involvement in lymphoma: prospective study in 116 patients and comparison with FDG-PET. *Eur. Radiol.* 23(8), 2271–2278 (2013).

Lymphomas are among the most common malignancies, and their staging according to the Ann Arbor criteria is of utmost importance for treatment and survival. The presence of lymphomatous cells in the bone marrow indicates the highest stage in the evolution of the disease. The standard method for assessing bone marrow involvement is blind bone marrow biopsy (BMB). However, this method is crude, invasive and highly subjected to error, as it is samples only a very limited region of the bone. For this reason, the authors performed several noninvasive imaging studies on a significant group of patients (116 cases) [1]. They performed whole-body MRI studies combined with FDG-PET on both aggressive and indolent lymphomas, in an attempt to identify the predictive value of both methods, using BMB as a reference.

The patients were selected from several clinics, under the care of several hematologists and the BMBs were interpreted by several hemopathologists. All the staff was blinded to the imaging findings. Also, the radiologist who interpreted the images was blinded for the BMB results, as well as the nuclear medicine specialist, who had no knowledge of the BMB or MRIs.

The results of this study demonstrated that whole-body MRI is not sufficient to replace BMB. FDG-PET was more sensitive for aggressive lymphomas, while less able to identify indolent ones. However, when combined, MR and PET-CT were able to demonstrate the bone marrow involvement in several BMB-negative cases. However, the

differentiation between aggressive lymphomas and indolent ones remains important, as the aggressive ones are readily identified by PET, while only BMB can identify bone marrow involvement in the indolent ones.

The study demonstrates the utility of combining MRI and PET data; however, only as complementary to BMB because their sensitivity is still too low.

Group selection and criteria for diagnosis were used in a highly skilled manner, even though the results are not definitive. This is a useful study, mainly for clinicians involved in cancer management.

Reference

1 Adams HJ, Kwee TC, Vermoolen MA *et al.* Whole-body MRI for the detection of bone marrow involvement in lymphoma: prospective study in 116 patients and comparison with FDG-PET. *Eur. Radiol.* 23(8), 2271–2278 (2013).

Radioisotope therapy of bone metastases

Evaluation of: Storto G, Gallicchio R, Pellegrino T *et al.* Impact of (18)F-fluoride PET-CT on implementing early treatment of painful bone metastases with Sm-153 EDTMP. *Nucl. Med. Biol.* 40(4), 518–523 (2013).

Bone cancer, both primary and metastatic, is usually accompanied during its evolution by severe pain, which further reduces the quality of life of the patient. This is generally due to the blastic or lytic lesions, which either induce compression at the place of the lesion or bore through bone, producing cavities that reduce its resistance. Most therapies are nowadays symptomatic, trying to alleviate pain with the means specific to algesiology, but there are several approaches that try to reduce the underlying causes of pain. Among these are chemotherapy surgery, external irradiation and biphosphonate chelators.

An effective tool for alleviating pain was discovered to be the chelator ethylenediamine tetramethylene phosphoric acid (EDTMP) complexed with 153-samarium (^{153}Sm), which has bone-seeking properties, thus depositing in areas with high bone turnover, such as tumor lesions. Furthermore, the radioactive samarium emits β particles with low energy, which are suitable for killing tumor cells without much irradiation of the surrounding tissue. It also has a low-energy gamma emission, which allows it to be tracked easily using a γ-camera.

The authors intended to combine PET-CT imaging with ^{153}Sm therapy, in order to obtain a better response to radiation therapy [1]. Starting from the hypothesis that for a bone lesion to become painful it has to be big enough to influence the surrounding tissues, they tried to begin therapy with ^{153}Sm before the appearance of clinical pain, based on images of potential lesions obtained with FDG-PET and classical technetium bone scans.

Whole-body scans were performed using ^{99m}Tc-diphosphonate, PET-CT with ^{18}FDG and, after Sm-EDTMP administration, a body scan for ^{153}Sm. Pain assessment was made using a visual analog scale (VAS), with ratings from 1 to 10. The patients were followed closely for 2 months after therapy.

The study demonstrated that early administration of samarium-EDTMP will significantly improve the outcome and quality of life in patients with bone metastases, even if these are not yet visible on ^{99m}Tc-diphosphonate bone scans. PET-CT was able to better identify skeletal metastases in patients where only the primary tumor was identified. PET was also able to identify sclerotic lesions with lower metabolic rates, due to the inflammatory reaction surrounding the site. Pain and suffering was much reduced in these patients and probably their survival was increased (not estimated owing to the limited duration of the study) due to early identification and suppression of metastatic foci in the bones.

This is a very good clinical study, with significant information that might prove of use for those clinicians that work in the field, as for all involved in imaging.

Reference

1 Storto G, Gallicchio R, Pellegrino T *et al.* Impact of (18)F-fluoride PET-CT on implementing early treatment of painful bone metastases with Sm-153 EDTMP. *Nucl. Med. Biol.* 40(4), 518–523 (2013).