An Appropriate Method of Measuring Bone Metastatic Subtypes by *In Vivo* Advanced Imaging from Clinical to Preclinical Study

Limin Fan

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Meiping Shi

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Jie Cao

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Hongchao Fu

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Jianzhong Su

shanghai first maternity and infant health hospital of Tongji university

Lanxiang Zhao

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Guangyu Tao

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Baofeng Guo

Shanghai longhua hospital of shanghai university of traditional chinese medicine

Mingcang Chen

Shanghai Institute of Materia Medica Chinese Academy of Sciences

Qiong Li

shanghai yuyang hospital of intergrated traditional chinese and weatern medicine of shanghai university of traditional chinese medicine

Liang Chen

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Bei Lei

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Cheng Chang

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Jianping Zhang

Shanghai Cancer Hospital: Fudan University Shanghai Cancer Center

Jianding Ye

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Sheng Liu

shanghai longhua hospital of shanghai university of traditional chinese medicine

Wenhui Xie

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

shunfang yang (✉ zyyg@sh163.net)

shanghai chest hospital <https://orcid.org/0000-0002-2663-4947>

Original research

Keywords: Lung cancer, Bone metastasis, Osteoblastic, Osteolytic, In vivo imaging, SPECT/CT, TMEM100, CDH1

Posted Date: January 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-145988/v1>

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Abstract

Purpose: Bone metastasis (BM) lesions are always considered to be non-measurable. In this study, we established a method that proved to be measurable the subtypes of BM by in vivo advanced imaging including bone scintigraphy (BS) and single-photon emission computed tomography (SPECT) with ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) fused computed tomography (CT), combined with skeletal radiography (XR).

Methods: One retrospective clinical audit was investigated on lung cancer patients who suffer from BM. The audit includes early static planar, later Whole-body skeleton images and a random sample of 198 patients who were performed on fusion of SPECT/CT scanners. Among them, 108 patients with BM were definite histologic diagnosed with lung cancer and 257 bone lesions were classified. A preclinical precision study developed a procedure of hot spot-based bone imaging screening experimental BM clone by performing anesthesia, intracardiac injection of five human lung cancer cells on the immunodeficient mice, reanimate, in vivo imaging and in vitro experiments (cell culture, histology, karyotype analysis, microarrays, real-time polymerase chain reaction assay (RT-PCR), and immunohistochemistry (IHC)). An osteolytic metastatic clone MDA-MB-231Bo (231Bo) was compared. Irradiation damage was tested.

Results: The clinical reports showed the incidence was primarily osteoblastic lesions, followed by mixed lesions and osteolytic. This study does not only confirmed the in vivo advanced imaging could be used to monitor and measure the subtypes of BM from clinical and preclinical data but also have ideal images (including movies), unique cell lines same as homo-sapiens, two markers associated with BM, TMEM100 and CDH1, as well as data from five pairs (BM clones and their parental cells) of lung cancer cells that released into GEO for further research. Ionizing radiation is controlled at its best.

Conclusion: The studies have demonstrated that bone lesions of 1mm or larger can be detected in mouse models. Osteolytic lesions were revealed that a flow of metastatic cells out of the destroying cortical bone gap to form a soft tissue tumor. This study and GEO data are applicable to the development of relevant research and treatments.

Full Text

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Figures

Figure 1

Representative images of three lung cancer patients with osteoblastic metastases, osteolytic and mixture of the two are shown, axial CT, axial SPECT, axial fused SPECT/CT, and maximum-intensity-projection (mip), respectively. The osteoblastic images of 50-y-old male with lung adenocarcinoma and the lesions in cross focus demonstrated osteoblastic BM. The osteolytic images of 62-y-old male with lung adenocarcinoma and the lesions in cross focus demonstrated osteolytic BM. The mixture images of 62-y-old male with human squamous cell lung carcinoma and the images indicated the lesions in mixed BM.

Figure 2

A procedure of selecting BM clone demonstrated the power of real-time, and repeatable in vivo imaging and in vitro experiments. Note: The implication of the color of this picture is: anesthesia with green means appropriate medication; Intracardiac injection with light green that the success rate of about 80%; Reanimation in pink indicates warming during resuscitation; Irradiation damage is expressed by cinnabar, and the dose of radioactive material is strictly controlled; Blue indicates appropriate imaging conditions; Light blue means meticulous and pollution-free.

Figure 3

Representative micro CT, SPECT, and fused SPECT/CT images (maximum-intensity projections), and XR of S8sx, MDA-231Bo, 776T, and A1BM tumor-bearing mice are shown, respectively. S8sx mouse with suspected lesions were revealed in mandible, right scapula, lumbar vertebra and left sixth rib by CT, SPECT, fused SPECT/CT, and XR after intracardiac inoculation for 19 day, respectively. Osteoblastic metastases were the main parts and osteolytic were rarely. MDA-231Bo mouse was revealed the

osteolytic metastasis of the fourth lumbar vertebra was lack of radioactive tracer, CT negative, SPECT, SPECT/CT and XR were positive, after intracardiac inoculation for 52 day. 776T mouse is denoted the lesions suffer severe bone cortex destruction after intracardiac inoculation for 40 day, CT, SPECT, fused SPECT/CT, and XR were demonstrated the osteolytic more than osteoblastic on mandible, radius, humerus, left rib, femur and tibia. A1BM series mouse was revealed the osteoblastic metastases in mandible, scapulae, thoracic vertebra and rib by SPECT and SPECT/CT, but CT and XR were negative, after intracardiac inoculation for 29 day. Note: The subtypes were classified according to the color of arrows in CT, SPECT, and XR: osteoblastic metastasis-light blue, osteolytic-light gray, mixture of two-orange. Color of arrow at the lesion location in fused SPECT/CT: mandible-dark red, scapula-yellow, thoracic and lumbar vertebra-gray, rib-red, cervical vertebra-light green, limb bone-brown. Suspicious lesion-pink. CT, Computer Tomography; SPECT, Single-photon Emission Computed Tomography; XR, skeletal radiography.

Figure 4

Fifteen highly expressed genes were screened by cDNA array

Figure 5

cRNA array clustering graph. The dark red and red lines are CDH1 and TMEM100, respectively 4, RT-PCR analysis

Figure 6

Figure 7

Representative images of micro CT, micro SPECT, and fused SPECT/CT showed rib micrometastases (the color of arrows: osteoblastic metastasis-light blue, osteolytic-light gray, mixture of two-orange, suspected lesion-pink; the lesion of rib-rad and scapula-yellow), the lesions were confirmed by relevant histopathology (supplementary Figure 8C, 9C and 9D), respectively. The pictures in the upper row are the images of rib lesion in the mouse loaded with 776T cells for 40 days revealed severe osteolytic metastases, and the middle and lower rows are the images of left 6, 8th rib lesions, and a right scapula lesion of tumor-bearing S8sx in the mouse at 19 days. CT, Computer Tomography; SPECT, Single-photon Emission Computed Tomography; 72°, 132° and 42° are the positions of the images in the captured GIF files (Supplementary movie 1-6), respectively.

Supplementary Files

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