Review Article

Advanced modalities of molecular imaging in precision medicine for musculoskeletal malignancies

ABSTRACT

Musculoskeletal malignancies consist of a heterogenous group of mesenchymal tumors, often with high inter- and intratumoral heterogeneity. The early and accurate diagnosis of these malignancies can have a substantial impact on optimal treatment and quality of life for these patients. Several new applications and techniques have emerged in molecular imaging, including advances in multimodality imaging, the development of novel radiotracers, and advances in image analysis with radiomics and artificial intelligence. This review highlights the recent advances in molecular imaging modalities and the role of non-invasive imaging in evaluating tumor biology in the era of precision medicine.

Keywords: Artificial intelligence, heterogeneity, molecular imaging, musculoskeletal, precision medicine, radiomics

INTRODUCTION

The number of new cancer cases in 2011–2015 was 439.2/100,000 persons/year, with approximately 163.5 cancer-related deaths/100,000 persons/year.[1] Cancers arise from complex biochemical cellular processes secondary to alterations in normal DNA, often resulting in uncontrolled rapid cellular proliferation. Tumor biomarkers are essential in the diagnosis, risk-stratification, and treatment planning of tumors. With the continual growing emphasis on genomics, proteomics, and radiomics, as well as advances in molecular imaging, personalized precision medicine is becoming a tangible reality. This manuscript aims to provide an overview of molecular imaging for musculoskeletal (MSK) malignancies, highlighting the role it may play in the era of precision medicine.

TUMOR HETEROGENEITY, GENOMIC BIOMARKERS, AND MOLECULAR IMAGING

Cancers consist of a heterogeneous collection of cell with various mutations, leading to different biologic properties, including degrees of differentiation and growth rate.[2,3] This heterogeneity serves as a strong internal mechanism for tumor cells to escape various oncologic treatments. Cancer cell heterogeneity can be categorized as intertumoral and intratumoral. Intertumoral heterogeneity alludes to various biological properties among different lesions of

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an identical malignancy. Intertumoral heterogeneity arises from a combination of intrinsic and extrinsic mechanisms, including genetic and epigenetic mutations and influences of the tumor microenvironment, causing varying biology of the same tumor type between patients or even different lesions within the same patient.[4] Intratumoral heterogeneity refers to the microheterogeneity within a tumor, in part secondary to imperfect rapid DNA replication in rapidly growing cancers. This leads to a diverse population of cancer cell types within a single lesion, creating difficulties in interpreting limited tissue sampling of a malignancy, such as a biopsy, and determining appropriate therapeutic management.[5,6]

Genetic mutations in tumors can consist of oncogenes (such as c-myc, fos, Ha-ras, Ki-ras, sis, met, SAS MFH, and MDM2), tumor suppressor genes (such as p53, Rb, NF1, and APC), and tumor-specific translocations (such as CHOP-FUS [TLS], EWS-FLI1, EWS-ATF1, SYT-SSX, and PAX3-FKHR).[3,7,8] Traditional medical management of tumors typically involves obtaining a single sample of a tumor and determining the appropriate therapeutic option from that encapsulating diagnosis. Precision medicine aims to capture both the inter- and intratumoral heterogeneity within a patient to create a personalized treatment plan. Molecular imaging noninvasively images the complex biochemical and genetic processes of cancers. This imaging consists of various physiologic imaging techniques targeting components such as peptides, antibodies, proteins, affibodies, aptamers, and nanoparticles, predominantly in the field of nuclear medicine, as well as analysis of quantitative data from cross-sectional imaging, such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US). Utilizing various imaging techniques, molecular imaging provides a realistic method to better quantify tumor heterogeneity throughout a patient.[9-11] Molecular imaging not only provides an insight into initial personalized cancer treatment decisions, but also allows for continual monitoring during treatment. This may lead to the detection of new cancer mutations during treatment, which could prompt changes in therapy before other signs of tumor progression.[12-15] With continuing improvements in molecular imaging techniques and devices, recognition of new genetic and molecular targets, and new methods of analyzing and quantifying data with artificial intelligence, there is an increasing role of molecular imaging in the diagnosis and treatment of MSK malignancies [Figure 1].

PHYSIOLOGIC IMAGING

Bone scintigraphy

Nuclear medicine bone scintigraphy, most commonly with the use of ^{99m}Tc-methylene diphosphonate (MDP), is a functional measurement of bone metabolism. It can play a significant role in the evaluation of osseous metastases and cancer staging, and help distinguish metabolically-inactive treated bone metastases from active disease. The specificity, sensitivity, and accuracy for bone scintigraphy for the detection of osseous metastases are 80.9%–96%, 67%–95.2%, and 60%–80.3%, respectively.[16] Bone scintigraphy can be performed with either a singlestatic phase to identify regions of bone with high osteoblast activity, or as a dynamic threephase study, with additional perfusion and blood pool phases to help distinguish inflammatory conditions and changes in blood supply. With a high sensitivity, bone scans are useful in identifying new metastatic lesions. However, the study is limited due to radiotracer uptake up by a variety of other disease processes, including metabolic bone diseases, infections, traumatic injury, and inflammatory conditions. [17-20]

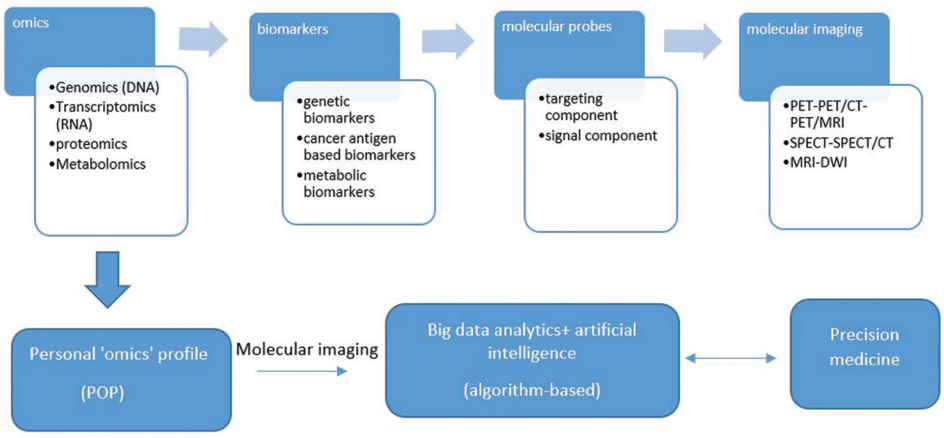

Figure 1: From omics to molecular imaging and precision medicine

Single-photon emission tomography

Single-photon emission computed tomography (SPECT) scans are spatial three-dimensional acquisitions of radionuclides. With multiplanar reconstruction, SPECT allows for better contrast resolution and improvement lesion localization. In addition, SPECT can be fused with CT to allow for concurrent anatomical and functional imaging, resulting in improved specificity, sensitivity, and spatial resolution for MSK malignancies.[21-23] In particular, SPECT-CT has been shown to reduce equivocal interpretations compared to SPECT or planar scintigraphy in MSK malignancies.[21,24-28]

Positron emission tomography

The development and advances in positron emission tomography (PET) have revolutionized functional imaging. With the use ^{18}F-fluorodeoxyglucose (^{18}F-FDG) to evaluate tumor metabolism, and various other radiopharmaceuticals targeting specific molecular targets, PET has now plays a big role in the accurate staging and monitoring of MSK malignancies, and can also serve as a predictor for treatment outcomes [Figures 2-4].[29-32]

Sarcomas are one of the less common malignancies, and despite current treatments, patients have poor outcomes and life expectancy.[33,34] ^{18}F-FDG uptake in sarcomas has

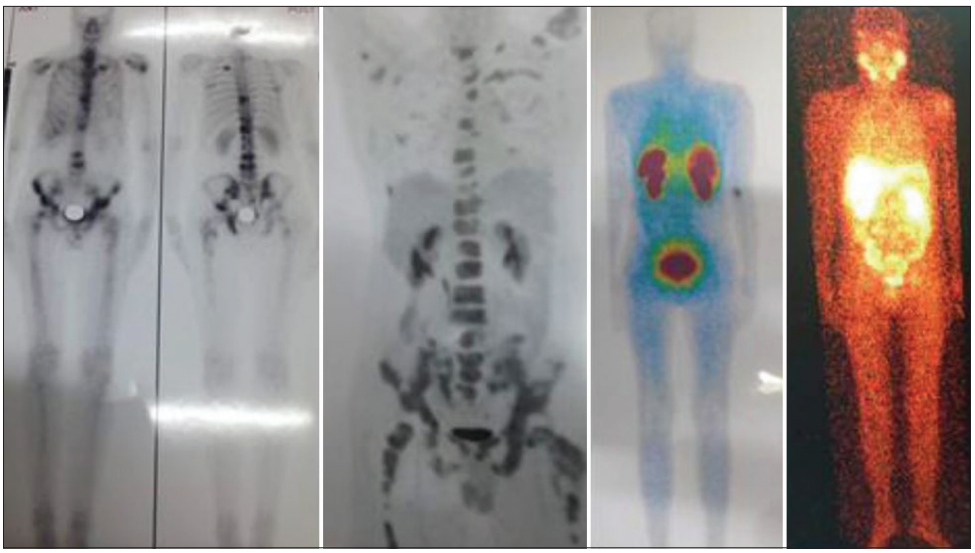

Figure 2: A 44-year-old man with carcinoma of unknown primary. The bone ^{99m}Tc-methylene diphosphonate scintigraphy demonstrated several skeletal lesions throughout the body, ^{99m}Tc-prostate-specific membrane antigen scintigraphy and ^{18}F-fluorodeoxyglucose positron emission tomography images showed avid lesions only in the pelvis, and ^{99m}Tc-octreotide scintigraphy demonstrated no activity, highlighting the intertumoral heterogeneity

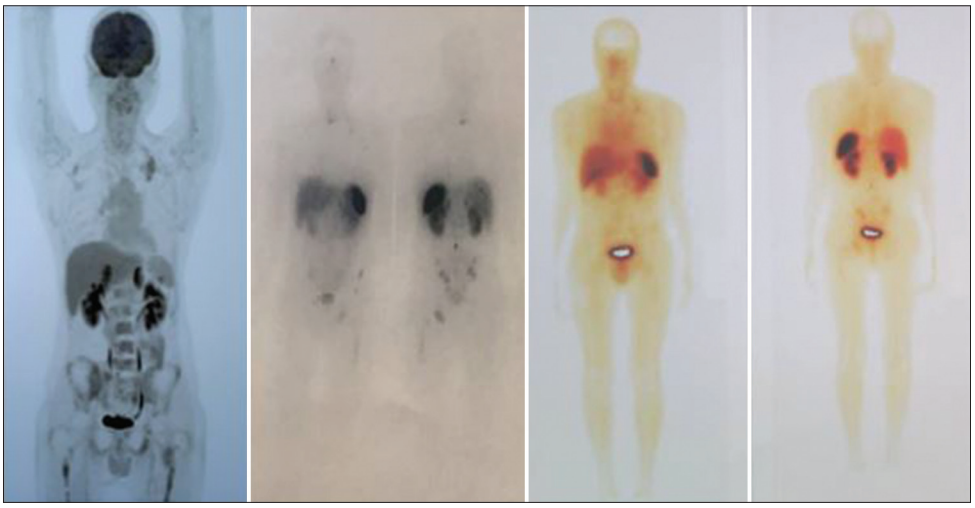

Figure 3: A 29-year-old man with poorly differentiated neuroendocrine tumor (Ki-67 = 28%). ^{99m}Tc-octreotide scintigraphy and post-^{177}Lu-DOTATATE therapy images showed intense uptake within the skeletal lesions, predicting a good response to ^{177}Lu-DOTATATE therapy in patients with somatostatin-expressing neuroendocrine tumors. However, ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography images demonstrated numerous ^{18}F-fluorodeoxyglucose-avid lesions throughout the skeleton and marrow, representing a poor prognosis

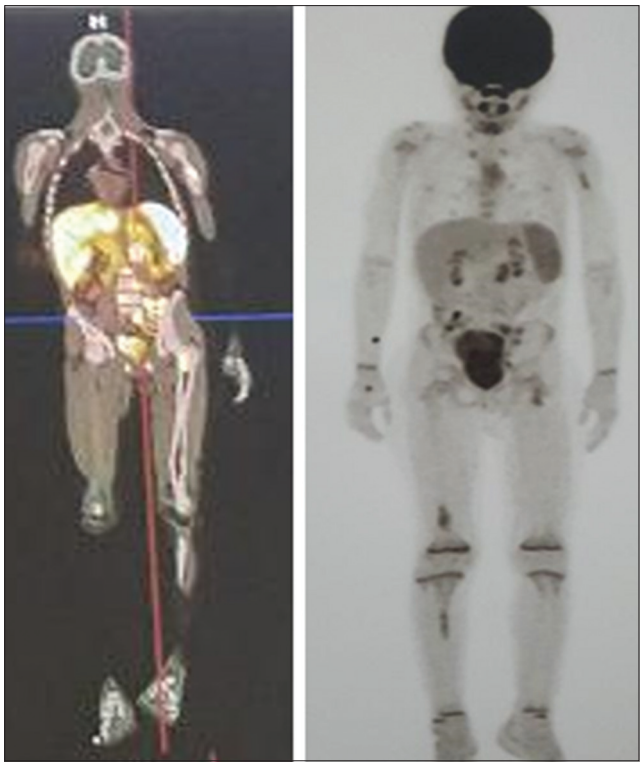

Figure 4: An 8-year-old boy with Stage IV neuroblastoma. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography images demonstrated faint-^{18}F-fluorodeoxyglucose-avid lesions throughout the skeleton (standardized uptake value <2), while ^{68}Ga-DOTATATE positron emission tomography-computed tomography showed numerous ^{68}Ga-DOTATATE-avid lesions in the same region (standardized uptake value >10)

been shown to be reflective of tumor biology and has a valid predictor for tumor aggressiveness and patient outcomes.[30,35] In addition, PET has a growing role in the evaluation of intra- and intertumoral heterogeneity.[36] Piperkova *et al*. demonstrated advantages of ^{18}F-FDG PET-CT for the initial staging, restaging, and evaluation of the treatment response for bone and soft-tissue sarcomas.[31] PET studies fused with cross-sectional imaging, PET-CT or PET-MRI, allow for more accurate disease localization, detection, and as a guide for biopsies.[37] Furthermore, ^{18}F-FDG PET-CT has been shown to better differentiate soft-tissue and osseous malignancies from benign lesions compared to PET or CT alone.[38-41]

In addition to ^{18}F-FDG, several novel PET radiotracers have shown promising results. ^{18}F-Fluoroestradiol, which targets estrogen receptors (ER) has been shown to have a high sensitivity for the detection of ER-positive skeletal metastases and is useful for quantifying *in vivo* ER expression without the need for biopsy.[42] Similar results have been seen for identifying osseous metastases of thyroid malignancy with ^{124}I.[43] ^{18}F-Fluorothymidine (FLT), a radiotracer which measures tumor proliferation, has shown promise in imaging bone and soft-tissue sarcomas. ^{18}F-FLT can help differentiate between high- and low-grade sarcomas and may be useful in evaluating changes in tumor biology over time and assessing intratumoral heterogeneity.[44] Furthermore, the use of dual tracer "cocktail scans" are actively being investigated. Iagaru *et al*. have shown increased detection of osseous metastases with combined ^{18}F-NaF and ^{18}F-FDG PET-CT compared to the modalities individually.[45-48]

Radiomics and artificial intelligence

Radiomics utilizes quantifiable data from imaging modalities to provide insight into tumor biology and heterogeneity. In the era of "-omics" this data can be combined with genetic and other data to obtain a comprehensive understanding of a patient's tumor biology. In addition, radiomics can aid in the diagnosis of tumor cell type, potentially negating the need for tissue biopsy in some cases and providing a better understanding of intratumoral heterogeneity, which is an intrinsic limitation of limited tissue sampling.[49-53] Imaging features analyzed with radiomics have been shown to have prognostic implications for a diversity of tumors.[54-57] In patients with soft-tissue sarcomas of the extremities, Vallières *et al*. demonstrated an association between extracted texture features from ^{18}F-FDG PET-CT and a propensity for developing lung metastases.[58] Radiomic MRI features have also been shown to help distinguish intermediate- and high-grade soft-tissue sarcomas.[59] Associations such as these aid in risk assessment at diagnosis and may help guide first-line therapy choices.

As this field continues to grow, and imaging databases become larger, new trends may arise from mining these large datasets. A current major limitation to the clinical applications of radiomics is the lack of effective autosegmentation techniques, with the majority of current studies performed with either manual or semi-automated segmentation. However, since machine learning techniques are becoming more sophisticated, the possibility of seamless autosegmentation in clinical practice is becoming more realistic.[51-55] Indeed, these algorithms and programs may soon be able to rapidly synthesize the imaging data with other clinical data points to provide even more diagnostic and prognostic information, allowing for more personalized treatment planning.[60-64]

CONCLUSION

Musculoskeletal malignancies have a wide array of intra- and inter-tumoral heterogeneity. With continued advances in molecular imaging, noninvasive methods of understanding tumor biology show promising results. This may aid in the diagnosis, prognosis, and treatment planning and monitoring of musculoskeletal malignancies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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