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Review

Development of imaging probes for bone cancer in animal models. A systematic review

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ABSTRACT

Bone is a dynamic tissue that is constantly remodeled throughout the lifetime to ensure the integrity of the skeleton. Primary cancer cells disseminate into circulation, often extravasating to bone, where they interact with the bone marrow to grow and proliferate, disrupting the bone homeostasis. Although primary bone tumors account for less than 0.2% of all cancers, bone is a common site for the development of metastases, as its microenvironment provides the necessary conditions for the growth and proliferation of cancer cells. Metastases to the skeletal system are observed in up to 70% of all cancer patients and the growth of disseminated tumor metastases is a major cause of mortality. As widely known, a non-invasive diagnosis of bone tumors at early stages is of great importance to provide insights that will help on the decision of therapy regimen, improving treatment outcomes. Early diagnosis of bone metastases is also an important step for establishing palliative care as they may cause serious endocrine, hematologic, neurologic and orthopedic complications as well as intolerable pain. Therefore, development of new imaging techniques, imaging moieties, and animal models to mimic these bone conditions, play an important role in improving the clinical outcome of this disease. In this review, we will briefly describe the advantages and disadvantages of the currently available imaging techniques that aim at identifying bone tumors. In addition, we will provide an update on the animal models applicable at mimicking bone tumor characteristics, as well as describe recent advances on the development of new imaging probes, in the preclinical settings including targeted nanoparticles and radiopharmaceuticals.

Contents

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1. Introduction

Primary bone tumors are uncommon and this has certainly contributed to the lack of data about their relative frequency and to the limited understanding of the risk factors. Overall, bone sarcomas represent 0.2% of all malignancies, and the prevalence rate for all bone and joint cancer is 0.9 per 100,000 persons per year [1,2]. The American Cancer Society's estimates, for 2016, about 3300 new cases and 1490 deaths from these cancers [2]. However, conditions that may simulate primary bone tumors, such as metastasis and non-neoplastic conditions (i.e. inflammatory processes, bone cysts and fibrous dysplasia) by far outnumber the cases of true bone tumors [3].

The main types of primary bone malignant tumors are osteosarcomas (OS), which occur mostly in the leg bones of children and young adults; chondrosarcomas, which usually afflict people over 40 years of age; and Ewing's sarcoma, a cancer that affects mainly children and teenagers [3,4]. Bone is also the third most common site involved in metastasis, behind lung and liver. Bone metastasis occurs in almost all tumors, with prostate, lung, and breast cancer most frequently implicated [5]. About 80% of patients with advanced breast or prostate cancer will eventually develop bone metastases during the course of the disease [6].

Available treatment options for bone cancer are surgery, radiotherapy and chemotherapy. Most patients need a combination of those methods. There are several different chemotherapeutic agents currently employed in the clinical settings, such as carboplatin, cisplatin, doxorubicin, etoposide and cyclophosphamide [7]. Among them, the bisphosphonates are the most efficient antiresorptives and are widely used for the treatment of diseases with increased number or activity of osteoclasts [8]. They have become the standard treatment for tumor-induced hypercalcemia and may play a role in preventing development of bone metastasis. Following administration, bisphosphonates bind avidly to hydroxyapatite (HAP) crystals of the bone matrix, reaching very high local concentrations in the resorption lacunae where they are internalized by the osteoclasts, thus causing apoptosis [5,6].

Besides that, radiopharmaceuticals have been used in the palliation of bone pain. In this sense, a variety of radioisotopes is available for clinical use, such as phosphorous-32, strontium-89, samarium-153 or rhenium-186 [5].

Diagnosis of bone cancer is based on patient symptoms, physical exams, imaging results and blood tests. A biopsy test is also needed in most cases to confirm cellular changes [2]. Imaging techniques are of great importance since are non-invasive methods that allow diagnosis, staging, response assessment and subsequent tumor surveillance during follow-up [9]. Different imaging tools, such as X-rays, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), optical imaging, single-photon-emission computerized tomography (SPECT) and positron emission tomography (PET) scans are currently being used to diagnose and follow-up bone disease [2].

Techniques such as CT, US, and MRI provide anatomical images with high resolution and detailed structural information. In contrast, radiopharmaceutical imaging, in particular PET, can give some functional information about the underlying tissues. However, these imaging modalities still have some limitations related to sensitivity and specificity. Furthermore, no single imaging strategy is consistently superior for the assessment of bone disease across all tumor types and clinical scenarios [10]. Therefore, is evident the need of refining these techniques, through faster and more sensitive instruments and/or through the development of novel imaging probes [9,11,12].

In this review, we briefly discuss the current role of imaging in clinical practice for bone cancer, describe some of the advances in imaging modalities currently undergoing evaluation, and provide an update, focused on small animals model, on new imaging probes for bone tumors that are currently in preclinical phase.

2. Bone tumors: causes, characteristics and consequences

Bone tumors can be classified as primary or metastatic. Among the primary bone tumors the most prevalent are OS, chondrosarcomas and Ewing's sarcomas. Other tumors, such as malignant fibrous histiocytoma, fibrosarcoma, giant cell tumor of bone and chordoma are also found in rare cases. As any other type of cancer, bone tumors present variable causes and associated risk factors, depending on the type of cell or region affected [2].

2.1. OS

OS are the most common primary bone tumor and, in opposition to other adult human cancers, lifestyle-related risk factors, such as body weight, physical activity, diet, and tobacco consumption seems not to be related to the development of this type of malignancy. OS develops especially during the teenage spurts, which suggests a link between rapid bone growth and risk of tumor formation [13].

Even though the exact cause of this tumor is unknown, several risk factors are associated, such as exposition to radiation therapy; presence of previous bone diseases (Paget disease, hereditary multiple osteochondromas); and inherited cancer syndromes, including retinoblastoma (mutation in RB1 gene) [14], Li-Fraumeni syndrome (mutation in TP53 gene) [15], Rothmund-Thomson syndrome (mutations in REQL4 gene) [16], Bloom syndrome (mutation in BLM gene), Werner syndrome (mutation in WRN gene) [17], and Diamond-Blackfan anemia (mutation in S19 and other ribosomal genes) [18].